The role of anti-inflammatory agents in the treatment of mood disorders

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Abstract

Background: Multiple reviews have demonstrated that mood disorders are associated with abnormal pro- and anti-inflammatory immunological markers and recent studies suggest that anti-inflammatory medication may play an important role in the treatment of mood disorders.

Aims:

1. To evaluate current evidence on the efficacy and acceptability of anti-inflammatory drugs in patients with major depressive disorder (MDD) and bipolar disorder.
2. To determine whether the anti-inflammatory tetracycline antibiotic minocycline, added to treatment as usual (TAU) for 3 months in patients with treatment-resistant depression leads to an improvement in depressive symptoms and if so, to estimate effect sizes to inform the development of a larger, hypothesis-testing study.

Methods: A systematic review and meta-analysis of published trials of anti-inflammatory agents in mood disorders was conducted. The Cochrane Central Register of Controlled Trials, PubMed, EMBASE, PsychINFO and Clinicaltrials.gov were searched from inception until April 15, 2017 for completed and on-going clinical trials of anti-inflammatory agents for MDD and bipolar disorder. Data from randomized controlled trials (RCTs) assessing the antidepressant and antimanic effect of adjunctive mechanistically diverse anti-inflammatory agents were pooled to determine standard mean differences (SMDs) compared with placebo and/or treatment as usual.

To address the second aim a multi-site, 12-week, double blind, placebo-controlled, pilot trial was conducted. The trial was of minocycline added to treatment as usual for patients suffering from DSM-5 major depressive disorder whose current episode has failed to respond to at least 2 antidepressants. The primary outcome measure was mean change in Hamilton Depression Rating Scale (HAMD-17) scores from baseline to week

12. Secondary measures were the Clinical Global Impression scale (CGI), Patient Health Questionnaire-9 (PHQ-9), the Generalised Anxiety Disorder scale (GAD-7) and EuroQoL (EQ-5D). Side effects checklists were also used. Minocycline was started at 100 mg once daily (OD) and increased to 200 mg OD after two weeks.

Results: The meta-analysis found that patients receiving anti-inflammatory agents showed lower post-treatment depressive symptom scores compared with those receiving placebo with a SMD of -0.71 (6 RCTs, n=214, 95% CI -1.24 to -0.17, p=0.009). Anti-inflammatory treatment was found to reduce post-treatment manic symptom scores with a SMD of -0.72 (3 RCTs, n=96, 95% CI -1.31 to -0.13, p=0.02). Anti-inflammatory treatment was found to yield an improvement in depressive symptom scores from baseline to outcome with a SMD of -0.52 (5 RCTs, n=194, 95% CI -1.01 to 0.05) but this was not statistically significant (p=0.07).

In the pilot RCT, a total of 41 participants were randomised, with 21 in the minocycline group and 20 in the placebo group. A large decrease in HAMD scores was observed in the minocycline group compared to the placebo group (Standardized effect size -1.21, $p < 0.001$). CGI scores in the minocycline group also showed a large improvement compared with placebo (OR: 17.6, $p < 0.001$). PHQ-9 (ES -0.43), GAD-7 (ES -0.46) and EQ-5D total (ES -0.48) showed more moderate improvements.

Conclusions: Anti-inflammatory treatments may confer benefit for both depressive and manic symptoms however current studies are limited by small sample sizes, short durations, differing baseline symptomatology and poorly defined illness durations. The findings of the pilot RCT indicate that adjunctive minocycline leads to improvement in symptoms of treatment-resistant depression. However, the findings require replication in a larger sample. Overall, further high-quality trials are needed before making recommendations for the routine clinical use of anti-inflammatory interventions including minocycline, in the treatment of mood disorders.

Declaration

I declare that I have composed this thesis and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

This thesis presents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are mine and not necessarily those of the NHS, the NIHR or the Department of Health.

The work presented in Chapter 3 was previously published in *Trials* as "Minocycline as an adjunct for treatment-resistant depressive symptoms: study protocol for a pilot randomised placebo-controlled trial" by MI Husain (author of thesis), IB Chaudhry (external supervisor), RR Rahman, AB Khoso, MM Hamirani, J Hodsoll, I Qurashi, JFW Deakin, N Husain and AH Young (internal supervisor). My supervisors and I conceived this study and I drafted the protocol for the study and prepared the manuscript for publication.

The work presented in Chapter 4 was previously published in the *Journal of Psychopharmacology* as "Anti-inflammatory treatments for mood disorders: systematic review and meta-analysis" by MI Husain (author of thesis), R Strawbridge, PRA Stokes and AH Young (internal supervisor). My supervisor and I conceived this study. I wrote the protocol for the systematic review, carried out database searches, conducted the quantitative meta-analysis and qualitative review of the literature as well as drafting the manuscript for publication.

The work presented in Chapter 5 was previously published in the *Journal of Psychopharmacology* as "Minocycline as an adjunct for treatment-resistant depressive symptoms: a pilot randomised placebo-controlled trial" by MI Husain (author of thesis), IB Chaudhry (external supervisor), N Husain, AB Khoso, RR Rahman, MM Hamirani, J Hodsoll, I Qurashi, JFW Deakin and AH Young (internal supervisor). My supervisors and I conceived this study and I carried out training and supervision of the research team as well as writing up the manuscript for publication.

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Chapter 1: Introduction

1.1 Prevalence of mood disorders and the burden of treatment resistance

Mood disorders i.e. major depressive disorder (MDD) and bipolar disorder are a leading cause of morbidity and mortality across the globe. Major depressive disorder was recently identified as the leading cause of ill health and disability worldwide (WHO, 2017). These conditions are frequently chronic and debilitating, often with poor recovery between episodes (Rush et al., 2006, Malhi et al., 2007, Marotta et al., 2015).

Accurate data on the prevalence of mood disorders does not exist for most countries and available evidence suggests that there is wide variability in prevalence estimates between countries. A systematic review of 18 prevalence and 5 incidence studies of mood disorders found significant variation across 1-year and lifetime prevalence of MDD and bipolar I disorder. The corresponding pooled rates for 1-year prevalence were 4.1 per 100 and 0.72 per 100, respectively. For lifetime prevalence, the corresponding pooled rates were 6.7 per 100 and 0.8 per 100, respectively (Waraich et al., 2004).

More recently there has been published data on the prevalence of ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th revision) depressive episodes in the WHO (World Health Organisation) World Health Survey across 60 countries. Twelve-month prevalence averaged 3.2% in participants without comorbid physical disease and 9.3% to 23.0% in participants with chronic physical health conditions (Moussavi et al., 2007). The WHO World Mental Health (WMH) Survey Initiative summarised 12-month prevalence estimates of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders 4th revision) major depressive episodes in 18 WMH countries ranged from 2.2% (Japan) to 10.4% (Brazil) (Kessler et al., 2010). The mid-point across all countries was similar to that in previous surveys (5%), as was the weighted average 12-month prevalence for the ten high-income (5.5%) and eight low and middle-income (5.9%) countries (Kessler & Bromet, 2013).

The WMH survey also provided data on the prevalence of bipolar disorder, which Merikangas et al., summarised in 2011. They reported that the aggregate lifetime prevalence of bipolar-I disorder was 0.6%, bipolar-II was 0.4%, sub-threshold bipolar was 1.4%, and Bipolar Spectrum (BPS) was 2.4%. Twelve-month prevalence of bipolar-I disorder was 0.4%, bipolar-II was 0.3%, sub-threshold bipolar was 0.8%, and BPS was 1.5% (Merikangas et al., 2011).

Although both depressive and manic symptoms are amenable to pharmacological treatments, a high proportion of patients neither responds nor achieves remission (Perlis et al., 2006, Rush et al., 2006, Vergunst et al., 2013). Many patients are also left suffering from a significant decline in their social and occupational functioning (Mahli et al., 2007). The Sequenced Treatment Alternatives for the Relief of Depression (STAR*D) study, a large naturalistic study of over 3500 patients with MDD showed that the response and remission rates with stage 1 treatment (i.e. the selective serotonin reuptake inhibitor citalopram) were 49% and 37%, respectively. Response rates over the subsequent next three treatment steps decreased to 16% and 13%, respectively, (Rush et al., 2006). A recent meta-analysis of current pharmacological treatments for depressive disorder in primary care showed only a relatively small effect size for antidepressant treatments when compared to placebo (Linde et al., 2015). Similarly, studies in bipolar disorder, such as the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed that only 58.4% of patients that receive adequate treatment according to current practice guidelines subsequently achieve partial or full remission (Perlis et al., 2006). It is therefore evident that there remains a significant need for more efficacious and novel treatment approaches.

1.2 Inflammation and its associations with mood disorders

In 1887 Julius Wagner-Jauregg was the first individual to study an association between the immune response and mental illness when he induced malaria in patients to alleviate symptoms of a condition called dementia paralytica. Dementia paralytica, also

referred to as “general paralysis of the insane”, led to cognitive decline, psychotic symptoms and paresis, which were later found to be the neuropsychiatric manifestations of cerebral syphilis (Raju, 1998). Since then there have been numerous studies linking inflammatory processes to a range of psychiatric illness, including MDD and bipolar disorder. Multiple reviews of clinical and pre-clinical data have clearly demonstrated that MDD and bipolar disorder are associated with abnormal profiles of circulating pro- and anti-inflammatory biomarkers in affected patients (Goldstein et al., 2009; Howren et al., 2009; O’ Donovan et al., 2013). Individuals with a raised inflammatory profile have been shown to have alterations in mood, sleep, energy, cognition, and motivation, all of which can form part of the presentation of a mood disorder. To understand putative aetiological models linking inflammation to mood disorders, it is important to discuss the functioning of the normal human immune and inflammatory response systems.

The immune response is divided into the innate and adaptive systems. The innate response is activated by pathogen associated molecular patterns (PAMPs), which cause the release of chemical factors including histamines, prostaglandins, bradykinin, serotonin, and leukotrienes (Abbas et al., 2012). Prostaglandins and thromboxanes are produced through the actions of enzymes calcium-dependent phospholipase A2 and cyclooxygenase (COX)-1 and 2, on arachidonic acid. These chemical factors produce the local inflammatory response causing signs and symptoms such as vasodilation and pain. They also attract macrophages to the site of inflammation. The macrophages release proteins called cytokines, such as Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-1 and IL-6, to initiate a systemic inflammatory response and adaptive immune response by attracting leukocytes and lymphocytes (Abbas et al., 2012).

The adaptive immune response creates and maintains the immune system's memory. T-lymphocytes produce a response to terminate cells identified as potentially pathogenic. They also stimulate cytokine release, to attract more macrophages, neutrophils and

lymphocytes. B-lymphocytes are also attracted and stimulated by the cytokines to produce antibodies against the pathogens (Abbas et al., 2012).

The cytokines and chemical factors produced during this inflammatory response can be used as biomarkers for investigating the potential association between inflammation and mood disorders. The evidence that mood disorders (or some subgroups thereof) are inflammatory-related disorders comes from multiple sources. These include a study demonstrating that peripheral administration of a pro-inflammatory cytokine (interferon-α, IFN- α) induces a depressive syndrome in many patients receiving it as a treatment for hepatitis (Van Gool et al., 2003). Treatment with cytokine IFN-α corresponds with the development of depressive symptoms in up to 45% of patients with no previous history of depression (Capuron & Miller, 2011).

Cytokines and chemokines are key regulators of immune function, with some of these mediators having a pro-inflammatory effect (e.g. interleukin-1 (IL-1), IL-12, and IL-18, tumour necrosis factor (TNF), interferon gamma (IFN-gamma)), whereas others are mainly anti-inflammatory (e.g. IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13) (Raison et al., 2006). Longitudinal studies have demonstrated that high plasma pro-inflammatory cytokine levels precede, and thus potentially cause depressive symptoms (Khandaker et al., 2014; Gimeno et al., 2009). However, emerging evidence indicates that this subdivision may be overly simplistic. For example, IL-6 may activate a classical pathway and a trans-signaling pathway, which may have predominantly anti- and pro-inflammatory activities respectively (Maes et al., 2014). In a recent systematic review and meta-analysis of eighty-two studies comprising 3212 participants with MDD and 2798 healthy controls there was a highly heterogeneous balance of peripheral levels of "pro-" vs. "anti-"inflammatory cytokines in individuals with MDD; levels IL-6, TNF-alpha, IL-10, the soluble IL-2 receptor, C-C chemokine ligand 2, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 were elevated in patients with MDD compared to healthy controls, whereas IFN-gamma levels were lower in MDD (Hedge's $g = -0.477$, $P = 0.043$) (Köhler et al., 2017).

Notwithstanding this, the most convincing evidence for a close relationship between inflammation and mood is the very frequent comorbidity of depressive symptoms with virtually all chronic inflammatory or autoimmune disorders (Capuron & Miller, 2011). Large proportions (probably greater than 50%) of patients with rheumatoid arthritis and systemic lupus erythematosus (SLE) have depressive or other psychiatric symptoms. Inflammatory physical disorders, both central and peripheral, are associated with greater rates of depression and in patients with Crohn's disease and comorbid depression, bouts of physical disease activity tend to co-occur with depressive episodes (Mardini et al., 2004). Although less robust, evidence also suggests that inflammation when present is associated with a more severe course of illness (Zalli et al., 2015), and more prominent in people whom are resistant to monoaminergic drugs (Carvalho et al., 2013; Grosse et al., 2015).

Bipolar disorder has also been proposed as a multi-systemic inflammation-related illness due to the significant inflammatory comorbidity associated with it (Leboyer et al., 2012). Several studies have demonstrated an association between bipolar disorder and inflammatory conditions including autoimmune disorders such as SLE (Perugi et al., 2014), chronic infections such as *Toxoplasma gondii* (Sutterland et al., 2015), cardiovascular disease (SayuriYamagata et al., 2017) and metabolic disorders such as diabetes, obesity and hypercholesterolemia (Perugi et al., 2014). Cytokine studies comparing patients with bipolar disorder to healthy controls have revealed elevated circulating levels of cytokines involved in both the innate (e.g. TNF-α, IL-6, IL-1 receptor antagonist (IL-1RA) and C-reactive protein (CRP)) and adaptive immune response (e.g. IL-4, IL-6 and IL-10) (Dargel et al., 2015; Goldsmith et al., 2016; Modabbernia et al., 2013; Munkholm et al., 2013a & b; Stuart & Baune 2014) in patients with bipolar disorder. Studies also demonstrate abnormal expression of other inflammatory chemokines, including those involved in the migration of neutrophils, monocytes and macrophages and several T-cell phenotypes (Bai et al., 2014, 2015; Barbosa et al., 2013; Bietzke et al., 2009; Drexhage et al., 2010 & 2011; O' Brien et al., 2006; Padmos et al., 2008). Consequently, patients with bipolar disorder have been shown to have abnormal

levels of neutrophils, monocytes and several T-cell subsets (Barbosa et al., 2015; Brambilla et al., 2014; Breunis et al., 2003; do Prado et al., 2013; Drexhage et al., 2011; Jakobsson et al., 2015; Kalelioglu et al., 2015; Tsai et al., 2012 & 2014).

Despite these associations, the direction of causality between mood disorder and systemic inflammation remains unclear. It is likely that the causality is multi-directional and that an abnormal inflammatory response, a mood disorder and inflammatory physical health comorbidities are all perpetuating factors for each other. Moreover, genetic and environmental risk factors for an abnormal inflammatory response may increase the risk of developing both a mood disorder and inflammatory physical health conditions.

1.3 Pathophysiological models linking inflammation to mood disorders

Although several putative aetiological models have been proposed to connect inflammation to mood disorders, the most consistent appears to be the cytokine hypothesis. As discussed earlier, pro-inflammatory cytokines have repeatedly been shown to be elevated in patients with mood disorders. These cytokines have been shown to affect central serotonin levels, the hypothalamic–pituitary–adrenal (HPA) axis, and microglial activation as well as brain structure (Rosenblat et al., 2014; Miller & Raison, 2016).

Reduced serotonin production and increased serotonin depletion are thus far the most commonly proposed mechanisms of mood disorder aetiology. In animal studies cytokines IL-6 and TNF-α have been shown to increase the breakdown of serotonin through facilitating its conversion to 5-hydroxyindoleacetic acid (Wang & Dunn, 1998; Zhang et al., 2001). Similarly, cytokines IL-2 and IFN have been shown to directly increase the activity of indolamine 2,3-dioxygenase (IDO), an enzyme that increases the conversion of tryptophan to kynurenine and consequently decreases the production of serotonin (Capuron et al., 2001, 2002 & 2003). Kynerenine, kynerenic acid and

quinolonic acid have also been shown to independently induce depressive and anxiety symptoms (Maes et al., 2011).

The physiological stress response induced by inflammation is known to activate the HPA axis and several studies have also shown that cytokines are involved in increasing levels of corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol (Brydon et al., 2009; Pace & Miller, 2009). Cytokines have also been shown to increase cortisol levels by blocking the negative feedback loop of the HPA axis by decreasing the expression, translocation and downstream effects of glucocorticoid receptors (Pace & Miller, 2009). Elevated cortisol levels have been shown to induce mood symptoms (Stetler & Miller, 2011). Although the exact mechanism is unclear, effects on serotonin function are again thought to play a part as cortisol increases hepatic tryptophan 2,3-dioxygenase (TDO) enzyme activity, leading to reduction in tryptophan, reduction in serotonin and increasing levels of kynerenine, kynerenic acid and quinolonic acid (Maes et al., 1990, 2011).

Interestingly, glucocorticoids are also known to have anti-inflammatory effects, which would contradict the hypothesis that they are involved in the inflammatory pathway that is responsible for the aetiology of mood symptoms. However, this is explained by the reduced hormone sensitivity and bioavailability of glucocorticoids while in an inflammatory state (Raison & Miller, 2003). Although serum cortisol levels increase in response to cytokines, it is proposed that the anti-inflammatory effect is suppressed because of cytokine-induced reduction in glucocorticoid receptor synthesis, translocation and binding. It is thought that cortisol still effectively activates TDO, thus decreasing serotonin levels and inducing mood symptoms (Maes et al., 2011).

Pro-inflammatory cytokines also have effects on microglial cells, which may also contribute to the maintenance of mood symptoms. Microglia are the macrophage cells in the central nervous system and are activated by cytokines TNF-α and IL-1β (Harry & Kraft 2012). Increased microglial activation has been associated with acute and chronic

mood episodes (Stertz et al., 2013). Release of TNF-α and IL-1β can cause microglial activation and activation of neuronal apoptotic pathways to induce synaptic pruning (Kraft and Harry, 2011). Prolonged synaptic pruning and neuronal apoptosis may be pathologic, destroying functional neuronal pathways and inhibiting the formation of new pathways. This may manifest with neuropsychiatric symptoms including mood symptoms as seen in MDD, bipolar disorder and other psychiatric disorders (Paradise et al., 2012; Stertz et al., 2013).

A raised inflammatory profile leading to a combination of serotonin dysfunction, disruption of the HPA axis and microglial activation may be responsible for impaired neuroplasticity leading to structural and functional brain changes in patients with mood disorders (Rosenblat et al., 2014; Miller & Raison, 2016). Although the underlying mechanism remains unclear, inflammation has been associated with structural and functional brain changes in humans including lateral ventricular enlargement, subgenual cingulate activity changes and decreased mesolimbic connectivity, all of which have also been implicated in the aetiology of MDD and bipolar disorder (Harrison et al., 2009; Kempton et al., 2011; Miller et al., 2013).

1.4 The potential role of anti-inflammatory agents in mood disorders

Given the substantial evidence linking the inflammatory cascade to mood disorders it would be logical to assume that the addition of an anti-inflammatory medication may be effective in the treatment of these conditions. Muller et al. were the first to demonstrate a reduction in depressive symptoms when using celecoxib, a COX-2 selective non-steroidal anti-inflammatory drug, in addition to reboxetine, for the treatment of MDD in a double-blind, randomised, placebo-controlled pilot study (Muller et al., 2006). Since then, there have been numerous trials of anti-inflammatory agents in mood disorders and reviews and meta-analyses have suggested that anti-inflammatory medication may play an important role in the treatment of mood symptoms (Faridhosseini et al., 2014, Fond et al., 2014, Kohler et al., 2014, Ayorech et al., 2015, Rosenblat et al., 2016). There is also some preliminary evidence that anti-cytokine treatment may have

antidepressant properties (Kappelmann et al., 2016). However, most trials of these agents are limited by small sample sizes, short duration of follow-up and significant clinical heterogeneity.

Warner-Schmidt et al. (2011) used the STAR*D dataset to determine whether nonsteroidal anti-inflammatory drugs (NSAIDs) could play a role in the treatment outcome of depressed individuals taking SSRIs and found that patients prescribed NSAIDs were more prone to be resistant to SSRI antidepressant medication. Thus, further work is needed in this area to clarify the role of inflammatory processes and anti-inflammatories in the treatment of mood disorders.

1.5 Minocycline as a candidate treatment for depression

As previously mentioned, numerous physiological mechanisms have been proposed to explain the link between inflammation and mood disorders, ranging from disturbed neurotransmission, disturbance in the biological mediators of stress (cortisol levels), activation of microglia and the release of neurotoxic metabolites leading to structural and functional brain changes. The tetracycline antibiotic minocycline has actions on a variety of these systems, although many of these are likely mediated through its anti-inflammatory effects. These actions include anti-oxidant, anti-apoptotic, and modulation of glutamate and monoamine neurotransmission (Hashimoto & Ishima, 2010; Soczynska et al., 2012).

Minocycline has a long half-life of 12–18 hours and is the most lipid-soluble of the tetracycline antibiotics, allowing for good penetration into the cerebrospinal fluid (CSF) and central nervous system (CNS) through the blood-brain barrier (Noble et al., 2009). It is usually well tolerated, has low propensity to produce antibiotic resistance and is commonly used to treat acne and other skin infections (Noble et al., 2009). It has been investigated in CNS diseases associated with inflammation such as multiple sclerosis, stroke and Parkinson's disease (Zhang et al., 2008; Zabad et al., 2007; Fagan et al., 2010 ;Fagan et al., 2011 ; Schabitz et al., 2008; NINDS NET-PD Investigators, 2008). Studies

have shown that a dose of 200mg daily in humans reduced the number of Gadolinium enhancing lesions in multiple sclerosis (Metz et al., 2004).

Biological mediators of stress, such as glucocorticoids, and peripheral inflammation have been found to trigger neuroinflammatory processes, of which microglia are thought to exert a central role (Frank et al., 2015). Minocycline is an inhibitor of microglial activation (Soczynska et al., 2012) and in pre-clinical studies has been shown to decrease depressive and anxiety-like behaviours in mice whist reducing levels of pro-inflammatory cytokines TNF-α and IL-1β. It has also been shown to normalise glucocorticoid levels through its actions on the HPA axis (Majidi et al., 2016).

Another inflammatory pathway that has been implicated in the pathophysiology of depression is the kynurenine pathway. Minocycline acts on this pathway and has been shown to block IDO activation without changes in brain serotonin (O'Connor et al., 2009). In a mice model of depression, minocycline has been shown to block the pro-inflammatory cytokine TNF-α, which activates IDO (Liu et al., 2015).

1.6 Rationale for a pilot RCT of minocycline for treatment-resistant depression

Studies in animal models have shown that minocycline may induce antidepressant-like effects. In a study involving both independent and co-administration of minocycline in rats, minocycline was shown to be effective in the Porsolt swim test. This test is centred on a rodent's response to the threat of drowning, and the result have been interpreted as measuring susceptibility to negative mood. It is commonly used to measure the effectiveness of antidepressants. Sub-threshold doses of both antidepressants and glutamate antagonists in combination with sub-threshold doses of minocycline were also shown to have antidepressant effects when considering the Porsolt swim test (Molina-Hernández et al., 2008).

In another pre-clinical study, learned helplessness was used as a model of depression and intracerebroventricular minocycline treatment was explored. The study found that

rats treated with minocycline had improved performance on the conditioned avoidance test (mild foot shock) and this did not correlate to changes in locomotor activity. This suggests the effects of minocycline are antidepressant. The study found biological correlates with serotonin turnover in the orbitofrontal cortex; being increased in rats with learned helplessness and this was not altered by minocycline treatment. However, there were no changes to serotonin in other brain regions investigated. No changes to dopamine levels were reported although the data suggested decreased dopamine levels in rats who acquired learned helplessness. Interestingly, although no deficit in dopamine was reported, minocycline caused an increase in dopamine levels in the amygdala. Finally, BDNF levels were reduced following the acquisition of learned helplessness and these remained unchanged following minocycline treatment (Arakawa et al., 2012).

In humans, there have been increasing data from open-label and pilot trials of minocycline use in psychiatric disorders, particularly in schizophrenia. A meta-analysis of six RCTs (minocycline n=215, placebo n=198) demonstrated minocycline's superiority versus placebo for reducing endpoint Positive and Negative Syndrome Scale (PANSS) total scores (SMD=-0.59; CI 95%=[1.15, -0.03]; p=0.04), negative (SMD=-0.76; CI 95%=[-1.21, -0.31]; p=0.001); general subscale scores (SMD=-0.44; CI 95%=[-0.88, -0.00]; p=0.05), Clinical Global Impressions scores (SMD=-0.50; CI 95%=[-0.78, -0.22]; p<0.001); and executive functioning (SMD=0.22; CI 95%=[0.01, 0.44]; p=0.04) in patients with schizophrenia (Solmi, 2017). All 6 studies included in this meta-analysis used minocycline 200mg/day as an augmentation strategy.

Specific to mood disorders, data from an open-label study of patients with psychotic unipolar depression suggested that minocycline 200mg daily added to standard antidepressant treatment was effective and well tolerated (Miyaoka et al., 2012). More recently an open-label pilot study in individuals with bipolar depression showed that adjunctive minocycline 200mg daily led to a reduction in depressive symptom severity from baseline to week 8 (Soczynska et al., 2017). A recent proof-of-concept study in 71

patients with unipolar depression (not necessarily treatment-resistant) receiving minocycline 200mg or placebo added to TAU found a 3-point change on the Montgomery-Asberg Depression Rating Scale (MADRS) in the minocycline group however this was not statistically significant. Nonetheless the minocycline group showed improvements in other outcomes suggesting that minocycline may be a useful adjunct to improve global experience, functioning and quality of life in depressed patients

The available evidence implicating neuroinflammation as a neurobiological underpinning for depression suggests that the addition of an anti-inflammatory medication such as non-steroidal anti-inflammatory drugs (NSAIDs) may be effective in the treatment of depression and indeed recent meta-analyses have suggested as much (Faridhosseini et al., 2014, Fond et al., 2014, Kohler et al., 2014, Ayorech et al., 2015, Rosenblat et al., 2016). However, NSAIDs such as celecoxib are associated with serious cardiovascular and gastrointestinal side effects (Wolfe et al. 1999, Mukherjee et al., 2011). Anti-cytokine drugs such as infliximab may also reduce severity of depressive symptoms in patients with a chronic inflammatory illness independently of improvement in physical illness treatment, but these drugs are also associated with potentially serious side effects and clinical trials in depressed patients are scarce (Kappelmann et al., 2016). Despite the potential antidepressant effects of minocycline, to date there have been no published clinical trials investigating the efficacy of minocycline in individuals with treatment-resistant depression.

1.7 Aims of thesis:

The aims of this thesis are:

1. To evaluate current evidence on the efficacy and acceptability of anti-inflammatory drugs in patients with major depressive disorder (MDD) and bipolar disorder.
2. To determine whether the anti-inflammatory tetracycline antibiotic minocycline, added to treatment as usual (TAU) for 3 months in patients

with treatment-resistant depression leads to an improvement in depressive symptoms and if so, to estimate effect sizes to inform the development of a larger, hypothesis-testing study.

Chapter 2: Overview of Methods

2.1 Introduction

This thesis is a compilation of three original research papers and this section provides an outline of my involvement in the studies and a brief overview of the methods employed in the published studies. I have provided a rationale for the use of each methodology below however detailed descriptions and discussions of methods for individual studies are provided in the three successive chapters.

The submission of the MD (Res) via publication is in accordance with King's College London regulations and was approved by the MD (Res) sub-committee at initial registration. The research programme was monitored through formal three-monthly progress reports and approved by the MD (Res) sub-committee review panel in 2017 based on an oral presentation of ongoing work, which covered the objectives, methodology and initial findings. The inclusion of specific publications from the related work was based on formal feedback and approval of the MD (Res) sub-committee.

I began my research programme in 2014 and collaborated with colleagues at the Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London as well as colleagues at the Pakistan Institute of Living and Learning to investigate the potential efficacy of anti-inflammatory agents in mood disorders. This thesis by publication contains the entire body of my research in this area, the majority of which was carried out between 2014 and 2017.

2.2 Methodology to address Aim 1

To determine the efficacy of anti-inflammatory drugs in improving both depressive and manic symptoms in patients with MDD and bipolar disorder a systematic review and meta-analysis of published randomised controlled trials of these drugs in patients with mood disorders was used. Systematic reviews and meta-analyses are the preferred method of summarising results of multiple primary studies by using strategies that limit

bias and random error, to identify a full sample of primary studies that can be summarised to produce a reliable estimate of the pooled treatment effect (Cook et al., 1997).

Systematic reviews differ from narrative conventional reviews by the presence of a specific methodology that describes a search strategy, specific inclusion and exclusion criteria and methods of data synthesis (Oxman & Guyatt, 1993; Cook et al., 1997). Meta-analysis is the method of data synthesis that allows the numerical pooling of results from multiple studies. Meta-analysis produces more precise estimates of the treatment effect than individual studies due to the larger sample sizes that result from pooling several trials. The larger sample sizes also lead to a reduction in random error (Higgins & Green, 2011).

Meta-analysis also provides valuable information on the variation or heterogeneity between individual studies, which is important to consider when interpreting results. It is helpful to distinguish between different types of heterogeneity. Variability in the participants, interventions and outcomes studied is called clinical heterogeneity, while variability in study design and risk of bias is methodological heterogeneity (Higgins & Green, 2011). Variability in the treatment effects being assessed in different trials is known as statistical heterogeneity, and is due to clinical or methodological variability, or a combination of both. Statistical heterogeneity presents when the treatment effects are more different from each other than one would expect due to chance alone. If there is evidence of significant statistical heterogeneity one can avoid pooling results and look for reasons for the heterogeneity, which could include methodological issues such as poor randomisation, early termination of trials, use of absolute rather than relative measures of risk, and publication bias (Higgins & Green, 2011).

2.2.1 Analytic methods used for the meta-analysis:

If all studies in the analysis were equally precise we could simply calculate the mean of the effect sizes. However, if some studies were more precise than others we would want

to assign more weight to the studies that carried more information. This is what is done in a meta-analysis. Rather than calculate a simple mean of the effect sizes a weighted mean is calculated, with more weight given to some studies and less weight given to others. However there are different analytic methods for assigning the weight of each study. Statistical models for pooling effect sizes in a meta-analysis are generally based on fixed or random effects models. The two models make different assumptions about the nature of the studies, and these assumptions lead to different definitions for the combined effect, and different mechanisms for assigning weights to each study (Borenstein et al., 2007).

The fixed effects model assumes that each study within a meta-analysis has the same underlying "true effect size" and that the combined effect is an estimate of this common effect size. In contrast, the random effects model does not assume that each study has the same effect, and it is assumed that the studies are a random sample of the relevant distribution of effects, and that the combined effect estimates the mean effect in this distribution (Borenstein et al., 2007). The decision on which approach to use is important when pooling results from studies with significant heterogeneity.

Under the fixed effect model all studies are estimating the same effect size, and so study weighting is determined entirely on the amount of information captured by that study. A large study would be given more weight, and a small study could be largely ignored. By contrast, the random effects model estimates the mean of a distribution of true effects. Large studies may yield more precise estimates than small studies, but each study is estimating a different effect size, and each of these effect sizes serve as a sample from the population whose mean we want to estimate. Therefore, as compared with the fixed effect model, the weights assigned under random effects can be considered more balanced. Large studies are less likely to dominate the analysis and small studies are less likely to be disregarded (Borenstein et al., 2007)..

Under the fixed effect model the only source of error in an estimate of the combined effect is the random error within studies. Therefore, with a large enough sample size the error will tend toward zero. This holds true whether the large sample size is confined to one study or distributed across many studies. By contrast, under the random effects model there are two levels of sampling and two levels of error. First, each study is used to estimate the true effect in a specific population. Second, all of the true effects are used to estimate the mean of the true effects. Therefore, the ability to estimate the combined effect precisely will depend on both the number of subjects within studies (first potential source of error) and also the total number of studies (second potential source or error). In other words, sample size does not affect the precision of the estimate of the mean in the random effects model (Borenstein et al., 2007).

For the purposes of the current meta-analysis, it was determined that use of a random effects model would be most appropriate, as there was evidence of significant statistical heterogeneity between studies. Furthermore, the majority of studies were of small sample size and overall there were a low total number of studies for each meta-analysis, meaning that use of the fixed effects model would increase the chances of error.

2.3 Methodology to address Aim 2

To determine the potential efficacy of minocycline as an adjunct to treatment as usual (TAU) in patients with treatment-resistant major depressive disorder, a 12-week, double blind, randomised, placebo-controlled pilot trial was conducted. Randomised controlled trials (RCTs) are the most appropriate study design to determine whether a cause-effect relation exists between treatment and outcome (Sibbald & Roland, 1998). The standard RCT in mood disorders compares the efficacy of a specific treatment with that of placebo for subjects identified according to prior criteria. It uses the parallel comparison of one or more treatments with placebo, with sample sizes considered adequate to detect a therapeutic signal, given the expected placebo response rates in that specific population (Tohen et al., 2015). Sample sizes are usually calculated using population effect sizes, calculated from previous trials of the intervention of interest.

When a true population effect size is unknown due to a paucity of trials of a particular treatment, pilot RCTs are often used to estimate effect sizes. Pilot RCTs are those studies in which the future, larger, hypothesis-testing RCT is conducted on a smaller scale (piloted) to see if it can be done (Eldridge et al., 2016). Pilot studies focus on the processes of the main study, for instance to determine whether recruitment, randomisation, treatment, and follow-up assessments all run according to protocol. They are also important in providing proof-of-concept and preliminary efficacy data to provide support for further phase II RCTs.

2.3.1 Analytic methods used for the RCT:

Since the validity of RCTs depends greatly on their design, conduct and reporting, it is important to use appropriate statistical methods when analysing the data from these studies. With regards to clinical trials six specific statistical issues need to be considered when developing a statistical analysis plan: baseline comparability of groups, selection of covariates for adjustment, covariate adjustment, intention-to-treat analysis (ITT), subgroup analysis and the handling of missing data. I will discuss how each of these issues were addressed for the pilot RCT included in this thesis.

2.3.1.1 Baseline Comparability

It has been argued that randomisation guarantees unbiased allocation of treatments to study participants but does not ensure for a particular trial that the patients or study participants in each treatment group will have similar characteristics (Altman, 1991). This suggests that randomisation gives unbiased treatment allocation, but not necessary balance. Some important covariates may not be balanced between treatment groups after randomisation, especially when the sample size is small and therefore usual practice in published clinical trial reports is to present baseline information on prognostic factors, as we have done for the included pilot RCT. Tests of significance that utilize a P-value to determine the statistical significance of the observed baseline difference in patients' characteristics are sometimes reported however this has been regarded as unnecessary (Burgess et al., 2003). The consensus regarding baseline

comparison of patients' characteristics appears to be that researchers should present the distributions of such baseline information of treatment groups in a table allowing readers to see the extent of similarities of the groups (Egbewale, 2015). We used this approach for summarizing baseline demographics and clinical data in the pilot RCT report.

2.3.1.2 Selection of covariates for adjustment

In order to account for baseline imbalances between treatment groups it is important to use an appropriate statistical method to adjust for covariates. The decision on which covariates to include often relies on the use of baseline tests of significance. In this case, study groups are compared in a wide range of baseline variables; those with statistically significant difference between groups are automatically accounted for in the analysis, and those that are not significant are ignored. Although this approach was commonly used previously, in recent years its use has been discouraged (Frayers and King, 2000) because it has been argued that following a robust randomisation process, it would appear redundant to again test whether the observed difference is purely by chance or not, which is what the test of significance does. Furthermore, disregarding baseline covariates that have prognostic influence but that are not significantly different between groups is also an argument against the use of hypothesis testing approach for covariate selection (Egbewale et al., 2014) since a significant imbalance will not matter if a factor does not predict outcome; whereas, a non-significant imbalance can benefit from covariate adjustment (Egbewale et al., 2014).

An important consideration for selection of covariates is prognostic strength and there are two ways in which this can be assessed. The first approach is to determine the prognostic importance based on the level of correlation between the particular covariate and the outcome variable with usual practice being that, if there is a weak correlation ($r < 0.3$), adjusting for the imbalance in such a covariate is not necessary even with a significant baseline difference in the covariate between the treatment groups (Egbewale 2015). Examining the strength of relationship between the baseline

and the outcome variables requires analysis of correlation between the covariates and the outcome of interest before deciding on selection of such covariates for adjustment.

The other approach when considering the prognostic importance of covariates is to include those that have been found *a priori* to be prognostic in relation to the outcome variable. This includes evidence of suitable covariate-outcome correlation ($r \geq 0.3$) from previous research (Egbewale et al., 2014). The decision on which covariate is selected for adjustment is taken before the trial starts and is specified in the protocol. Adjustment of covariates identified *a priori* also includes statistically adjusting for stratification or minimisation factors. For the purposes of the pilot RCT, we had decided on inclusion of some variables *a priori,* although these were not listed explicitly in the published protocol. These included baseline outcome scores, treatment contrast (minocycline or placebo), time and interactions between time and treatment to allow treatment estimates to differ at 2, 4, 8 and 12 weeks.

2.3.1.3 Covariate adjustment

Randomisation may not ensure balance in some important covariates which may make it difficult to interpret the results of statistical tests for the treatment effect (Tu et al., 2004). Thus, it is important that any imbalances are corrected or adjusted. Methods for controlling the covariate imbalance can either be at the design stage or during statistical analysis. Adjustment at the design stage includes the use of minimisation and stratification. Adjustment during statistical analysis is carried out by using relevant statistical analysis models. Many clinical trials use both design methods that reduce covariates imbalance and statistical adjustment during analysis simultaneously.

In the case of a single post-treatment assessment of a continuous outcome variable, methods for adjustment at the statistical analysis stage include: 1) change score analysis that determines group effect based on the difference between the baseline and the post treatment score (basic adjustment) 2) analysis of covariance, which is a model-based adjustment that includes the baseline of the outcome variable in the model. Statistical

adjustment can also be performed by the use of logistic regression or by pooling the stratified analyses, using, for example, a Mantel Haenszel test (Egbewale 2015). Statistical adjustment achieves more valid treatment effect estimates and significance tests (Assmann et al., 2000).

Although the main reason for adjustment of covariates is to minimise the occurrence of a chance finding, it may also lead to greater power of the trial (Egbewale et al., 2014). In our pilot RCT all continuous measures, including the primary outcome HAMD scores were analysed with linear mixed models to account for the dependencies in the data from the repeated measures. CGI was an ordinal outcome and so a generalised linear mixed model (proportional odds) was used for this outcome. Explanatory variables in the model were baseline outcome scores, treatment contrast (minocycline or placebo), time and interactions between time and treatment to allow treatment estimates to differ at 2, 4, 8 and 12 weeks.

2.3.1.4 ITT analysis

Intention-to-treat (ITT) analysis is the strategy for the analysis of RCTs that compares participants in terms of the groups to which they were originally randomly assigned (Hollis and Campbell, 1999) meaning that participants are always analysed in the group to which they were initially randomised even if they drop out of the study (Hollis and Campbell, 1999). ITT analysis is widely considered as the most appropriate analysis set for the primary effectiveness analyses of any phase III clinical trial since it assesses the overall clinical effectiveness most relevant to the real-life use of the intervention.

The Consolidated Standard of Reporting Trials (CONSORT) statement recommends that authors should indicate whether analyses were performed on an ITT basis (Begg et al., 1996) and we ensured that we followed this guideline when conducting the pilot RCT. The most appropriate way to deal with all forms of protocol violation is to apply ITT to include patients who receive a treatment other than the one allocated, and patients who do not adhere to treatment.

Per-protocol analysis is another method used (often as a secondary evaluation) in which participants who have not adhered to the allocated intervention are excluded. It only describes the outcomes of the participants who adhered to the research protocol. Per-protocol analysis is problematic when the reasons for non-adherence to the protocol are related to prognosis (Montorri and Guyatt, 2001). We know that participants who adhere to treatment tend to do better than those who do not adhere, even after adjustment of co-variates, therefore excluding participants that do not adhere from the analysis leaves only those who are likely to have a better outcome and leads to bias.

2.3.1.5 Subgroup analysis

Subgroup analyses allow comparisons of treatment outcomes for participants subdivided by baseline strata to determine whether treatment difference in outcome (or lack of it) depends on certain characteristics of participants. Subgroup analyses are important if there are potentially large differences between stratified groups in the risk of a poor outcome with or without treatment, if there are practical questions about when to treat, or if there are doubts about benefit in specific groups (e.g. the elderly). Since participants recruited into a clinical trial are not a homogeneous sample, their response to treatment and the differing impact on them of different treatments may vary, in ways that influence choice of treatment (Pocock et al., 2002).

However, most trials only have sufficient statistical power to detect the overall main effect difference in response between treatment groups, so that if subgroup effects do exist, they may well go undetected because the trial was not large enough (Pocock et al., 2002). Smaller sample sizes within subgroups lead to greater standard errors and reduced power relative to the overall clinical trial, resulting in an increased risk of a type II error; whereas, the multiplicity of hypotheses tests that results from examining multiple subgroups will lead to an increased risk of a type I error (Altman, 1991). The suggested approach to a sub-group analysis is to compare the difference between the treatments for the sub-groups of interest within an appropriate multiple regression

model. We had initially planned on conducting a subgroup analysis of differences in biomarker levels between the minocycline group and the placebo group in our study, however given the amount of missing biomarker data, the analysis of biomarkers was restricted to a descriptive analysis only.

2.3.1.6 Handling missing data

Even in a well-designed and controlled study, missing data occurs in almost all research. Missing data present various problems. First, the absence of data reduces statistical power. Second, the lost data can cause bias in the estimation of parameters. Third, it can reduce the representativeness of the samples. Fourth, it may complicate the analysis of the study. Each of these issues can damage the validity of the trials and can lead to invalid conclusions.

Rubin (1976) first described and divided the types of missing data according to the assumptions based on the reasons for the missing data. In general, there are three types of missing data according to the mechanisms of missingness.

i. Missing completely at random

Missing completely at random (MCAR) is defined as when the probability that the data are missing is not related to either the specific value which is supposed to be obtained or the set of observed responses. The statistical advantage of data that are MCAR is that the analysis remains unbiased. Power may be lost in the design, but the estimated parameters are not biased by the absence of the data.

ii. Missing at random

Data are regarded as Missing at random (MAR) when the probability that the responses are missing depends on the set of observed responses, but is not related to the specific missing values which is expected to be obtained. This is the assumption that was applied in our pilot RCT.

iii. Missing not at random

If the characters of the data do not meet those of MCAR or MAR, then they fall into the category of missing not at random (MNAR). The cases of MNAR data are problematic. The only way to obtain an unbiased estimate of the parameters in such a case is to model the missing data. The model may then be incorporated into a more complex one for estimating the missing values.

The best possible method of handling the missing data is to prevent the problem from occurring in the first place by well-planning the study and collecting the data carefully. However when data is missing despite these efforts, statistical methods such as the Last Observation Carried Forward (LOCF), Multiple Imputation and Maximum Likelihood approach can be used. For the pilot RCT, our statistician used the Maximum Likelihood approach to handle missing data. This method does not impute any data, but rather uses each cases available data to compute maximum likelihood estimates. The maximum likelihood estimate of a parameter is the value of the parameter that is most likely to have resulted in the observed data (Hox, 1999).

When data are missing, we can factor the likelihood function. The likelihood is computed separately for those cases with complete data on some variables and those with complete data on all variables. These two likelihoods are then maximized together to find the estimates. This method gives unbiased parameter estimates and standard errors but an advantage over Multiple Imputation is that it does not require the careful selection of variables used to impute values that Multiple Imputation requires (Hox, 1999). By using the likelihood approach in the analysis of the data from the pilot RCT, we found that socio-economic status at baseline was a predictor of missingness of outcomes. Socio-economic status was therefore included in all the primary analysis models.

2.4. Contribution to each published peer-reviewed paper

2.4.1 Paper 1: Husain MI et al. (2015) Minocycline as an adjunct for treatment-resistant depressive symptoms: study protocol for a pilot randomised controlled trial. *Trials*, Sep 15;16:410. doi: 10.1186/s13063-015-0933-5.

This is the published study protocol for the pilot randomised controlled trial of minocycline as an adjunct for treatment-resistant depressive symptoms. I drafted the protocol for the trial under the supervision of my supervisors. The development of the protocol helped inform the completion and submission of the ethics application, which was approved in March 2014. Following ethical approval, I registered the trial on Clinicaltrials.gov and as first author, wrote the manuscript for this paper. I submitted the manuscript and made all necessary amendments that were suggested following a detailed peer review process, under the guidance of my supervisors, Professors Chaudhry and Young. The protocol was also presented as a poster at the International Society of Bipolar Disorders annual meeting in Toronto, Canada in June 2015.

2.4.2 Paper 2: Husain MI et al (2017) Anti-inflammatory treatments for mood disorders: Systematic review and meta-analysis. *Journal of Psychopharmacology*, Sep; 31(9):1137-1148. doi: 10.1177/0269881117725711. Epub 2017 Aug 31.

For the systematic review and meta-analysis, I developed a study protocol under the supervision of Professor Allan Young. This was registered on the PROSPERO database for systematic review protocols. I then undertook a systematic search of relevant databases using the search criteria in the protocol. After searches were complete I scanned abstracts of potentially relevant studies and used the study inclusion and exclusion criteria to shortlist papers. If a second opinion was required regarding a study's inclusion, this was sought from my co-authors. After shortlisting studies I constructed tables to extract data pertaining to the primary and secondary outcomes from each study. This was done in collaboration with one co-author (Rebecca Strawbridge). Two co-authors (Professor Young and Dr. Paul Stokes) completed the quality assessments for each of the included studies. After extracting the data I used the

Revman software to conduct a quantitative meta-analysis. My co-author Rebecca Strawbridge undertook meta-regression analysis and supported me with measurement of publication bias. As first author I wrote the manuscript for the review and submitted the paper for publication. In collaboration with my co-authors I made necessary corrections to the manuscript after the peer review process.

2.4.3 Paper 3: Husain MI et al. (2017) Minocycline as an adjunct for treatment-resistant depressive symptoms: A pilot randomised placebo-controlled trial. Journal of Psychopharmacology, Sep;31(9):1166-1175. doi: 10.1177/0269881117724352. Epub 2017 Aug 31.

This was a multi-site, 12-week, individually randomised, parallel group, double blind, placebo-controlled, pilot trial of minocycline added to treatment as usual for patients suffering from a DSM-5 major depressive episode that had failed to respond to at least two antidepressant treatments. The study was conducted in Karachi, Pakistan, and participants were recruited from outpatient psychiatric clinics at Abbasi Shaheed Hospital, Karwan-e-Hayat Hospital, Civil Hospital, and the Institute of Behavioural Sciences between October 2014 and March 2016.

My role as chief investigator in this study was to provide scientific leadership and oversight to the research team in conjunction with my supervisors. As mentioned previously I developed the protocol for the study, completed and submitted the application for ethical approval and registered the study to a clinical trial database. I chaired bi-weekly Skype meetings to provide supervision to the research assistants and trial managers. Along with my supervisors I provided research training and workshops to the research team during annual visits to Pakistan. Once data collection was complete, I worked with my co-author, Dr John Hodsoll to analyse the data. I was also involved in dissemination of the findings from this study and submitted a poster of preliminary results at the joint International Society of Bipolar Disorders/International Society of Affective Disorders biennial meeting in Amsterdam, Netherlands in July 2016. As first author I wrote the manuscript for the study and submitted the paper for

publication. After a rigorous peer review process, I worked on amendments to the manuscript under the supervision of my supervisors.

Chapter 3: Published study protocol

Husain *et al. Trials* (2015) 16:410
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TRIALS

STUDY PROTOCOL Open Access

Minocycline as an adjunct for treatment-resistant depressive symptoms: study protocol for a pilot randomised controlled trial

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Abstract

Background: Depression is one of the leading causes of disability worldwide. A high proportion of patients do not respond to standard drug treatments. Recent evidence has suggested that anti-inflammatory treatment may have beneficial effects in major depression. Minocycline is a tetracycline antibiotic with good CNS penetration that exerts effects on multiple interacting symptoms implicated in the pathophysiology of mood disorders. Open-label studies have suggested that minocycline is effective as an adjunct drug in improving depressive symptoms.

Methods/Design: This is a multi-centre, 3-month, double-blind, placebo-controlled, pilot trial of minocycline added to treatment as usual for patients suffering from DSM-IV major depressive disorder. This will be a double-blind, randomised, controlled, two parallel-arm study with 20 participants in each arm, giving a total of 40 participants. There will be a screening visit, a randomization visit and four follow-up visits. Clinical assessments using the Hamilton Depression Rating Scale (HAM-D), Clinical Global Impression scale (CGI), Patient Health Questionnaire-9 (PHQ –9) and the Generalised Anxiety Disorder scale (GAD-7) will be carried out at every visit. Side effects checklists will also be undertaken at each visit. Biomarkers (inflammatory cytokines and CRP) will be measured at baseline and at the end of the treatment phase. Minocycline will be started at 100 mg once daily (OD) and will be increased to 200 mg at two weeks.

Discussion: Anti-inflammatory treatments have been shown to have some beneficial effects in the treatment of major depressive disorder. The aim of this pilot randomised controlled trial is to establish the degree of improvement in depressive symptoms with the addition of minocycline to treatment as usual.

Trial registration: ClinicalTrials.gov NCT02263872 registered 10 October 2014.

Keywords: Depression, Major depressive disorder, Minocycline, Anti-inflammatory

Background

Major depressive disorder is associated with significant morbidity and mortality. Depression is the leading cause of disability worldwide in terms of years lost due to disability [1]. Although depressive symptoms are amenable to antidepressant treatment, a high proportion of patients neither responds adequately nor achieves remission. For example in the Sequenced Treatment Alternatives for the Relief of Depression (STAR*D) study, the response and remission rates with stage 1 treatment (citalopram) were 49 and 37 %, respectively. The further response rates decreased to 16 and 13 %, respectively, over the subsequent next three treatment steps [2]. More recently, a systematic review of the efficacy of current pharmacological treatments of depressive disorder in primary care showed only a relatively small effect size for antidepressant treatments when compared with the placebo [3]. Thus, there remains a clear need for exploring novel treatment approaches.

Recently, there have been promising preclinical and clinical data linking inflammatory processes to a range of psychiatric illness including depression. The evidence

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that depression (or some subgroups thereof) is an inflammatory-related disorder comes from multiple sources, including the observation that depression is associated with raised inflammatory markers in the absence of a medical illness [4]. More specifically, depression has been associated with higher levels of positive acute phase proteins (APPs) and low levels of negative APPs [5], as well as increased levels of complement factors C3c and C4 and immunoglobulin M (IgM) and IgG [6]. Inflammatory medical illnesses, both CNS and peripheral, are associated with greater rates of depression and in patients with Crohn's disease and comorbid depression, bouts of physical disease activity tend to co-occur with depressive episodes [7]. Furthermore, patients treated with cytokines for various illnesses have an increased risk of developing depressive illness [8]. For example, treatment with cytokine IFN-α corresponded with the development of depressive symptoms in up to 45 % of patients [9].

The available evidence suggests that the addition of an anti-inflammatory medication may be efficacious in the treatment of depressive illness. Muller et al. [10] demonstrated a reduction in depressive symptoms when using Celecoxib, a COX-2 selective non-steroidal anti-inflammatory drug, in addition to Reboxetine, for the treatment of major depressive disorder in a double-blind, randomised, placebo-controlled pilot study. A recent meta-analysis showed that augmentation with Celecoxib is an effective add-on treatment for unipolar depressive patients [11]. However, other studies have found that anti-inflammatories may have an antagonistic effect on the antidepressant actions of SSRIs [12]. Further work is needed in this area to clarify the role of inflammatory processes and anti-inflammatories in the treatment of depression.

The tetracycline antibiotic minocycline has been proposed for the treatment of depressive symptoms as well as negative symptoms in schizophrenia [13, 14]. Preliminary data from an open-label study of patients with psychotic unipolar depression suggested that minocycline augmentation of antidepressant treatment was effective and well tolerated [15]. Minocycline is a pleiotropic agent that exerts effects on multiple interacting systems (that is, anti-inflammatory, anti-oxidant, anti-apoptotic, glutamatergic and monaminergic) implicated in the pathophysiology of mood disorders. Despite such neuroprotective properties, there have been no published clinical trials to date investigating the antidepressant effects of minocycline in individuals with major depressive disorder.

In this double-blind, randomised, controlled pilot trial, we will determine the efficacy of minocycline as an adjunct to treatment as usual (TAU) in patients with major depressive disorder. We hypothesise that minocycline augmentation will lead to an improvement in depressive symptoms in participants in comparison with the placebo.

Aim

The aim of this study is to investigate whether the addition of minocycline to treatment as usual (TAU) for 3 months in patients with major depressive disorder will lead to an improvement in depressive symptoms compared with TAU.

Methods/Design

Overview

This is a multi-centre, 12-week, double-blind, placebo-controlled, pilot trial of minocycline added to treatment as usual for patients suffering from DSM-IV major depressive disorder. It will be a double-blind, randomised, controlled, two parallel-arm study with 20 participants in each arm, giving a total of 40 participants. The study will be conducted in Karachi, Pakistan, and participants will be recruited from outpatient psychiatric clinics at the following units: the Karwan-e-Hayat Hospital, Abbasi Shaheed Hospital, Civil Hospital Karachi and Institute of Behavioural Science, Karachi.

All patients will give written informed consent after reading the information provided in Urdu. Treatment as usual (TAU) will comprise medications including antidepressants (SSRI's, Tricyclics, MAOIs, and SNRIs), mood stabilisers (with the exception of valproic acid) and antipsychotics, as well as psychotherapy and other psychosocial interventions.

Randomisation and masking

Tablets will be dispensed by a single pharmacy in Karachi according to separate computerised randomisation lists generated using an online randomisation tool (www.randomisation.com) and will be held by a central pharmacist in Pakistan. There will be no further stratification.

Patients, their families, referring psychiatrists and the research assistants carrying out the assessments will be blind to the study drug until the completion of the study. Reign Nutro Pharma and Jawed Traders (Pakistan) will provide minocycline and placebo in identical tablet form, matched both for colour and size.

Sample size

Participants will be randomly divided into two groups: the intervention group and treatment-as-usual group. A total of forty participants will be recruited and divided equally into two arms. This is a pilot trial, and therefore, the sample size is sufficient for a study of this nature. Assuming an attrition rate of 10 %, we are confident that we will have at least 18 subjects per group for analysis at the end of the trial. The U.S. Food and Drug Administration guidance on drug study design recommends that a minimum of 12 subjects per group is sufficient for pilot trials [16].

Power calculation

In the proposed study, a group size of 18 participants is powered at 0.75 and an alpha of 0.05 to detect an effect size of 0.75 in the reduction of Hamilton Depression scores (HAM-D) [17] between the minocycline and treatment as usual. At present, there are no clinical trials of minocycline in the treatment of unipolar or bipolar depression; therefore, a true population effect size is currently unknown. However in clinical trials with antidepressants, an effect size of 0.40 or higher is considered a clinically significant response criterion [18].

Local research ethics committee approval

Institutional review board (IRB) approval has been obtained from the ethics committee of the Karachi Medical and Dental College and Dow University of Health Sciences, Pakistan.

Inclusion criteria

Inclusion criteria are (1) patients aged 18 to 65 years, (2) Diagnostic and Statistical Manual-IV (DSM-IV) diagnosis of major depressive disorder, (3) competent and willing to give informed consent, (4) taking the current antidepressant medication for a minimum of 4 weeks (6 weeks for Fluoxetine) prior to baseline, (5) the current episode of depression has failed to remit with at least two courses of antidepressant treatment (one of which is the current course), (6) able to take oral medication and (7) if female, willing to use adequate contraceptive precautions and to have monthly pregnancy tests.

Exclusion criteria

Exclusion criteria are (1) relevant medical illness (renal, hepatic, cardiac, serious dermatological disorders such as exfoliative dermatitis, systemic lupus erythematosis), (2) prior history of intolerance to any of the tetracyclines, (3) concomitant penicillin therapy, (4) concomitant anticoagulant therapy, (5) presence of a seizure disorder, (6) currently taking valproic acid, (7) any change of psychotropic medications within the previous 4 weeks, (8) diagnosis of substance abuse (except nicotine or caffeine) or dependence within the last 3 months according to DSM-IV criteria, (9) pregnant or breast-feeding or (10) presence of primary psychotic disorder.

The criteria for leaving the trial are (1) patient's request, (2) at the discretion of the responsible medical officer or investigator (for example, an adverse event or poor compliance) and (3) pregnancy.

Study procedure

Recruitment

The psychiatry consultants responsible for patient care will be approached and asked if they will allow their patients to take part in this research study.

In the first instance, the research clinician will approach the clinical teams to inform them about the research study, especially with regard to inclusion and exclusion criteria. The research clinician will establish good working relationships with the individual clinical teams. They will be in regular contact either by phone or by visits to determine, in collaboration with the clinical team, if the patients are suitable to take part in the research study. If patients meet the entry criteria, are clinically stable and the consultant psychiatrist and the clinical team agree the patient could be a possible participant, the consultant will introduce the study to the patient. With the patient's agreement, the research clinician will visit the patient to explain the research study verbally and provide them with the patient information sheet. After the patient has had time to read and understand the patient information sheet (at least 24 h) and is willing to take part, a meeting (visit one) will be set up with the patient in order to obtain signed informed consent for the research and also signed consent for the research team to have access to their medical notes.

Screening visit

Confirmation of patient suitability will be carried out at this point. Participants recruited to the trial will undergo structured diagnostic interviews using the Mini International Neuropsychiatric Interview (MINI) to confirm a diagnosis of DSM-IV major depressive disorder [19]. This tool has been validated for use in the local Urdu language and has been used in previous studies [20]. The Hamilton Depression Scale (HAMD-17) [17] will be used to measure severity and response and is not being utilised as a screening tool for this study and therefore there is no specific HAMD-17 score required for study inclusion. Other Inclusion/Exclusion criteria will be checked at this visit and confirmation of consent and pregnancy testing, if appropriate will be carried out.

Follow-up

Participants will be randomised to receive minocycline or treatment as usual (TAU). Patients will continue with their current antidepressant treatment prescribed by their psychiatrists. Minocycline added to TAU will start at a dose of 100 mg daily and will be increased after two weeks to 200 mg daily, taken as a single dose to encourage compliance.

The patients' day-to-day care will remain the responsibility of the consultant psychiatrist or other mental health professional in charge of the patient. However, research assistants will maintain contact throughout the study in order to respond to any concerns or changes in circumstances or mental or physical state. Contacts will be 2-weekly for the duration of the study. Any study-related safety concerns will be the responsibility of the co-investigators who can be contacted at any time through the research team.

Outcome measures

The primary clinical outcome measures will be mean change from baseline to week 12 on the Hamilton Depression Scale scores [17]. Response is defined as a reduction of 50 % or more of the HAMD-17. Remission is defined as a score of ≤7 of the HAMD-17.

Ratings will be made on the basis of a semi-structured clinical interview at baseline, weeks 2, 4, 8 and 12.

The secondary clinical outcome measures will be the Clinical Global Impression (CGI) scale, a 7-point overall measure of severity; the PHQ −9 [21], a depression severity measure; and the GAD-7 [22], a measure of generalised anxiety disorder. These instruments have been used in a previous clinical trial in Pakistan [23]. Participants will also complete the Mood Disorder Questionnaire (MDQ) [24], a brief self-report questionnaire to screen for bipolar disorder. Adverse effects will be monitored using a rating scale that has been specifically designed for minocycline. This rating scale has been used by the authors in previous studies [14].

Biomarkers

Participants will be asked to provide two blood samples for research analysis. The provision of blood samples is optional and does not affect participation in the trial. These samples will be collected at baseline and at week 12. The samples will be collected to investigate the relation of the minocycline to the inflammatory markers and if this relates to the subjective experience of symptom change. The biomarkers tested include complete blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Research assistant training and inter-rater reliability

Research assistants in Karachi were trained in Structured Clinical Interview for DSM-IV (SCID) and clinical assessments at the University of Manchester for a previous grant-funded study. Interrater reliability will be measured throughout the study by local PIs. To establish inter-rater reliability training videos will be used while two raters code them independently. SPSS will then be used to calculate the Intraclass Correlation Coefficient.

Statistical analysis

All analyses will be based, as far as possible, on the intention-to-treat principle (with weighting adjustments to allow for differential loss to follow-up). Primary and secondary outcomes will be measured using a mixed-effects model (ANCOVA).

Study coordination

The study will be coordinated through weekly meetings by local investigators. There will be two weekly tele- or video-conferences with the chief investigator.

Dissemination

Outcomes will be reported in a peer reviewed journal (publication target Journal of Psychopharmacology) and will also be communicated at relevant conferences and local newspapers for general audience.

Discussion

Depression remains a leading cause of morbidity and mortality globally. Standard pharmacological treatments often have poor response leading to diminished social and functional outcomes. The consequential financial burdens of untreated or partially treated depressive symptoms on the individual and wider society are significant. Recent studies indicate that anti-inflammatory treatments may have some beneficial effects in depressive disorder. A previous open-label study and case reports indicate that the use of minocycline as an adjunct to antidepressants may provide some evidence of a reduction in depressive symptoms.

To date there are no controlled clinical trials that have investigated the use of minocycline for the treatment of depressive symptoms. Our pilot randomised controlled trial is the first of its nature and the findings from it may contribute to evidence in the management of patients with treatment resistant depressive symptoms. Should our results show a trend that minocycline reduces depressive symptoms, we will use them to inform the development of a larger trial. We hope that the current pilot study will determine the feasibility of recruitment, randomization, intervention implementation, blinded assessment procedures and retention for a larger scale hypothesis testing study. In the long term, we hope the findings of this study will contribute to the treatment of patients who suffer from prevalent and often debilitating illness.

Trial status

This clinical trial was registered in October 2014. The study is currently recruiting participants. The estimated study completion date is August 2016. Please refer to this study by its ClinicalTrials.gov identifier: NCT02263872.

Abbreviations

ANCOVA: analysis of covariance; CGI: Clinical Global Impression Scale; DSM-IV TR: Diagnostic and Statistical Manual-IV; GAD-7: Generalised Anxiety Disorder-7 Questionnaire; HAMD: Hamilton Depression Rating Scale; MDQ: Mood Disorder Questionnaire; PHQ-9: Patient Health Questionnaire-9; PI: Principal Investigator; RA: Research Assistant; TAU: treatment as usual.

Competing interests

IBC, JFWD and NH have given lectures and advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, Astra Zeneca and Janssen pharmaceuticals for which they or their employing institution have been reimbursed. RR and MMH have received educational grants and support for academic meetings from Pfizer, Roche, Novartis and Nabigasim. AHY has been commissioned to provide lectures and advice to all major pharmaceutical companies with drugs used in affective and related

disorders. AHY has undertaken investigator-initiated studies from Astra Zeneca, Eli Lilly, Lundbeck and Wyeth.
None of the companies have a financial interest in this research.

Authors' contributions

MIH conceived the idea for the study, contributed to design of the study, is involved in training and supervision of the RAs and drafted the manuscript. IBC conceived the idea for the study, contributed to design and coordination of the study and is involved with training and supervision of the RAs. RR contributed to the design of the study, recruitment of patients, is doing assessments and is involved with training and supervision of the RAs. MMH contributed to the design of the study, recruitment of the participants and is doing assessments. IQ contributed to the design of the study and drafted the manuscript. ABK is contributing to the recruitment of the patients and is doing assessments. JFWD contributed to the design of the study and drafted the manuscript. NH conceived the idea for the study, contributed to the design and coordination of the study, and is involved in assessments and in training and supervision of the RAs. AHY conceived the idea for the study, contributed to design of the study and drafted the manuscript. All authors read and approved the final manuscript.

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Chapter 4: Published systematic review and meta-analysis

Review

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Anti-inflammatory treatments for mood disorders: Systematic review and meta-analysis

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Abstract

Background: Recent studies suggest that anti-inflammatory medication may play a role in the treatment of mood disorders.

Aims: The purpose of this study was to determine the efficacy of anti-inflammatory drugs in patients with major depressive disorder and bipolar disorder.

Method: The Cochrane Central Register of Controlled Trials, PubMed, EMBASE, PsychINFO and Clinicaltrials.gov were searched from inception until 15 April 2017 for completed and on-going randomized controlled trials of anti-inflammatory agents for major depressive disorder and bipolar disorder. Data from randomized controlled trials assessing the antidepressant and anti-manic effect of adjunctive mechanistically diverse anti-inflammatory agents were pooled to determine standard mean differences (SMDs) compared with placebo and/or treatment as usual.

Results: Patients receiving anti-inflammatory agents showed lower post-treatment depressive symptom scores compared with those receiving placebo with a standard mean difference of −0.71 (six randomized controlled trials, n=214, 95% CI −1.24 to −0.17, p=0.009). Anti-inflammatory treatment was found to reduce post-treatment manic symptom scores with a standard mean difference of −0.72 (three randomized controlled trials, n=96, 95% CI −1.31 to −0.13, p=0.02). Anti-inflammatories did not show a statistically significant improvement in the secondary outcome measure (change in symptom scores from baseline to outcome).

Conclusions: Further high quality trials are needed before making recommendations for the routine clinical use of anti-inflammatories in the treatment of mood disorders.

Keywords

Depression, bipolar disorder, inflammation, anti-inflammatory

Introduction

Mood disorders are a leading cause of morbidity and mortality. Major depressive disorder (MDD) and bipolar disorder cause significant disability worldwide (Whiteford et al., 2013). These conditions are frequently chronic and debilitating, often with poor recovery between episodes (Malhi et al., 2007; Marotta et al., 2015). Despite advances in the treatment of mood disorders, current treatments are often not effective and may be poorly tolerated due to adverse effects (Geddes and Miklowitz, 2013; Linde et al., 2015; Rush et al., 2006; Vergunst et al., 2013). There remains a clear need for new treatment approaches. Recently promising data has indicated that inflammation may play an important role in mediating mood disorders. Multiple reviews have demonstrated that MDD and bipolar disorder are associated with abnormal pro- and anti-inflammatory immunological markers (Baumeister et al., 2014; Dowlati et al., 2010; Goldstein et al., 2009; Howren et al., 2009). The evidence that mood disorders (or some subgroups thereof) are inflammatory-related disorders derives from multiple sources including the observation that both MDD and bipolar disorder are associated with raised inflammatory markers in the absence of a physical illness (Baumeister et al., 2014; Dantzer et al., 2008; Munkholm et al., 2013; O'Donovan et al., 2013; Song et al., 1994). Recent evidence indicates that inflammatory changes with pharmacological treatment may differ based on clinical outcome: while interleukin (IL)-6 appears to reduce with pharmacological treatment, tumour necrosis factor (TNF)α levels may only decrease in treatment responders (Strawbridge et al., 2015). This is supported by a trial identifying improvements in clinical response to infliximab (a TNFα antagonist) in MDD patients with high levels of inflammatory markers (Raison et al., 2013).

Recent reviews and meta-analyses have suggested that anti-inflammatory medication may play an important role in the treatment of mood symptoms (Ayorech et al., 2015; Faridhosseini et al., 2014; Fond et al., 2014; Kohler et al., 2014; Rosenblat et al., 2016). However, meta-analyses have only evaluated the efficacy of these compounds for a specific disorder (e.g. bipolar disorder or MDD), and only for depressive symptoms (Kohler et al., 2014; Rosenblat et al., 2016). There has been significant research outputs from trials

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of anti-inflammatory agents in mood disorders since the literature search for the most recent meta-analyses was completed and in view of the on-going challenges posed by treatment resistance in mood disorders, (Geddes and Miklowitz, 2013; Linde et al., 2015; Rush et al., 2006; Vergunst et al., 2013), there remains a need to update the evidence-base for the use of novel treatments including anti-inflammatory medication. No meta-analyses have yet assessed anti-inflammatory treatments for mania. Furthermore, combining studies of both bipolar and unipolar depression may have the advantage of investigating inflammation as a trans-diagnostic target for multiple neuropsychiatric disorders; few studies have directly compared inflammation in unipolar and bipolar depression but there do not appear to be marked differences between these subpopulations (Goldsmith et al., 2016; Su et al., 2011) and increases in statistical power can be achieved by considering the two together.

The primary aim of this systematic review and meta-analysis is to determine the efficacy of anti-inflammatory drugs in improving both depressive and manic symptoms in patients with MDD and bipolar disorder. The review was registered on the PROSPERO database for systematic reviews and it is reported here following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2015).

Method

Search strategy

We searched the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, PsychINFO and the National Institute of Health website Clinicaltrials.gov from inception until 15 April 2017. Searches were not restricted by language. Citation lists of relevant studies and reviews were also checked for relevant trials. The authors of significant papers over the last five years and other experts in the field were also contacted and asked if they were aware of any additional studies.

The following search string was used: ((depression) OR (major depressive disorder) OR (depressive symptoms) OR (bipolar disorder) OR (mania) OR (manic symptoms)] AND [(anti-inflammatory) OR (NSAID) OR (acetylsalicylic acid) OR (cyclooxygenase 2 inhibitor) OR (COX-2) OR (antibiotics) OR (celecoxib) OR (infliximab) OR (etanercept) OR (minocycline) OR (N-acetyl cysteine) OR (NAC)] AND [(trial) OR (RCT) OR (treatment)).

Inclusion and exclusion criteria

Studies included were restricted to randomised controlled trials and crossover trials with male and female participants of all ages who met International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) (WHO, 1992) or Diagnostic and Statistical Manual of Mental Disorders 5th revision (DSM-5) (American Psychiatric Association, 2013) criteria for MDD or bipolar disorder. Trials with ICD 9 and DSM III/IIIR/IV/IVR diagnoses approximating to these codes were also included. All subtypes of major depressive and bipolar disorder were included. Dysthymia and cyclothymia were excluded. Clinical trials that measured depressive symptoms in patients with physical health comorbidities who did not meet criteria for MDD or bipolar disorder (i.e. not experiencing a current depressive, hypomanic or manic episode) at baseline were also excluded.

For the purposes of this review, anti-inflammatory treatments are defined as non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX)-2 inhibitors, pro-inflammatory cytokine inhibitors, N-acetyl cysteine (NAC) and minocycline hydrochloride. Minocycline has effects on multiple interacting systems (including inflammatory and oxidative pathways) that are thought to be involved in the pathophysiology of mood disorders (Soczynska et al., 2012). NAC has also been included as an anti-inflammatory treatment since recent evidence shows that it modulates pathophysiological processes including oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction and neuroinflammation (Dean et al., 2011).

Other agents such as polyunsaturated fatty acids (Appleton et al., 2010), statins (O'Neil et al., 2012), the antidiabetic drug pioglitazone (Kashani et al., 2013; Sepanjnia et al., 2012; Zeinoddini et al., 2015) and the nutritional supplement curcumin (Ng et al., 2017) have all been proposed as agents with supposed anti-inflammatory and antidepressant actions. However, as the anti-inflammatory effects of these agents are only considered to be putative, they were excluded from the present meta-analysis. In light of the evidence supporting their anti-inflammatory action, drugs included in this review were: ibuprofen, aspirin, diclofenac, naproxen sodium, celecoxib, anti-tumour necrosis factor (TNF)-α (etanercept, infliximab, adalimumab), ustekinumab, NAC and minocycline. We included studies where anti-inflammatories were administered in trials either as single or adjunctive therapy (in cross-over trials). The minimum length of therapy for inclusion was one day. Criteria for maximum length of therapy or length of follow-up were not stipulated. Anti-inflammatory treatments were compared with: placebo, antidepressant treatment, mood stabiliser treatment, combination treatment (e.g. antidepressant and mood stabiliser) and other treatments e.g. antipsychotic medication.

Outcome measures

The primary outcome measure was the effect of anti-inflammatory drugs in the treatment of acute mood symptoms. If more than one symptom measure was provided in a particular study, the primary outcome measure for the study was preferred to other measures.

For depressive episodes, treatment effects were measured by: severity of depressive symptoms at endpoint as measured by validated depressive symptoms rating scales (Beck's Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Inventory of Depressive Symptomatology (IDS)). Secondary outcome was changes (from baseline to endpoint) in validated depressive symptom rating scales (BDI, HAM-D, MADRS and IDS).

For manic episodes, efficacy of treatment was measured by: severity of manic symptoms at endpoint as measured by validated manic symptom rating scales (Young Mania Rating Scale (YMRS), Altman Self-Rating Mania Scale (ASRM)). Secondary outcome was changes (from baseline to endpoint) in validated manic symptoms rating scales (YMRS, ASRM).

Data extraction

All studies generated from the systematic search were evaluated against the pre-defined inclusion criteria by one review author

(MIH). Abstracts for these studies were screened and irrelevant studies excluded. Full texts for all studies that met the inclusion criteria were obtained. Any disparities were addressed by reaching consensus between review authors (RS, PRAS and AHY). Data extraction was conducted by two review authors (MIH, RS) and included description of participants, description of the intervention and control groups, psychometric data and outcomes. Two review authors (PRAS, AHY) undertook quality assessments. The bias risks of the randomised clinical trials included were addressed based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* using the Quality Assessment Tool for Quantitative Studies (Effective Public Health Practice Project, 1998; Higgins and Green, 2011). Study data quality was assessed in six domains: presence of selection bias, strength of study design, presence of confounders, blinding of outcome assessors, strength of data collection methods and reporting of withdrawals and drop-outs. Disagreements were resolved via further discussion with a third review author (RS).

Statistical analysis

Data was entered in to the Review Manager (Revman version 5.3) (Cochrane Collaboration, 2011) software program by one review author (MIH). Meta-analyses were conducted where data were available for ≥3 studies per main comparison. The main comparisons were anti-inflammatory treatment versus placebo or placebo added to treatment-as-usual (TAU). The primary outcome assessed was severity of mood symptoms at treatment endpoint measured using a pooled effect size of depressive/manic symptom scores between patients treated with adjunctive anti-inflammatory agents compared with those treated with adjunctive placebo and/or TAU.

Other outcomes included changes (from baseline to endpoint) in validated depressive and manic symptom rating scales. Sensitivity analyses comparing anti-inflammatories to placebo and/or TAU for unipolar depression and bipolar depression were undertaken.

Pooling of effect sizes and tests of heterogeneity were conducted using Review Manger 5.3 software. Cohen's *d* effect sizes were calculated using continuous variables to determine the standardised mean difference (SMD) of change in depression scores for placebo-controlled trials. SMD was also calculated for post-treatment symptoms severity scores as a secondary outcome measure. A random effects model was used (DerSimonian and Laird, 1986). Heterogeneity of analyses was assessed using the I^2 statistic which indicates the proportion of effect size variance likely due to study heterogeneity (Higgins et al., 2003). To further explore the sources of heterogeneity, meta-regressions were undertaken on the main comparisons to account for study quality, baseline symptom severity, and length of treatment. Meta-regressions utilised a restricted maximum likelihood (REML) method for estimating model parameters. The likelihood of publication bias was also assessed for the main comparisons using Egger's test (Egger et al., 1997) in comparisons that contained at least 10 studies.

Results

Using our search criteria, 9053 records were identified. Following inspection of abstracts, 23 suitable papers were identified and the full-texts were assessed (see Figure 1). Nine of these papers were then excluded from the quantitative meta-analysis for the following reasons: (a) they reported outcomes (i.e. cognitive symptoms and suicidal ideation respectively) that did not pertain to overall mood symptom severity (Dean et al., 2012; Waterdrinker et al., 2015); (b) full results could not be obtained despite efforts to contact the authors (Berk et al., 2012, 2014; Halaris et al., 2014; Mousavi et al., 2017; Raghuvanshi et al., 2013); (c) they reported results of a secondary analysis of a primary study (Magalhães et al., 2011a); 4) they did not have a placebo/TAU arm (Mohammadinejad et al., 2015). A total of 14 studies were therefore included in the meta-analysis whilst the excluded studies were included in the qualitative analysis.

Study characteristics

Tables 1 and 2 present study characteristics for each trial. Included studies randomised 847 participants ranging from 30–269 per study. Studies were conducted in the USA (Nery et al., 2008; Raison et al., 2013), Iran (Abbasi et al., 2012; Akhondzadeh et al., 2009; Arabzadeh et al., 2015; Emadi-Kouchak et al., 2016; Jafari et al., 2015; Kargar et al., 2015; Majid et al., 2015; Mousavi et al., 2017; Saroukhani et al., 2013), Germany (Müller et al., 2006) and Australia (Berk et al., 2008, 2012, 2014; Magalhães et al., 2011a,b, 2013). Seven RCTs investigated MDD, four RCTs investigated bipolar depression and three investigated manic/hypomanic symptoms. Only one RCT included patients under the age of 18 years (Mousavi et al., 2017).

Eleven studies investigated the COX-2 selective non-steroidal anti-inflammatory drug, celecoxib (Abbasi et al., 2012; Akhondzadeh et al., 2009; Arabzadeh et al., 2015; Halaris et al., 2014; Jafari et al., 2015; Kargar et al., 2015; Majid et al., 2015; Mohammadinejad et al., 2015; Mousavi et al., 2017; Müller et al., 2006; Nery et al., 2008) and three studies investigated N-acetyl cysteine (Berk et al., 2008, 2012, 2014), although there were several secondary analyses published based on one of these original trials (Dean et al., 2012; Magalhães et al., 2011a,b, 2013; Waterdrinker et al., 2015). We included one study investigating the cytokine inhibitor infliximab (Raison et al., 2013), one investigating aspirin (Saroukhani et al., 2013) and one investigating minocycline (Emadi-Kouchak et al., 2016). Length of treatment varied from 6–24 weeks (mean 10.57, standard deviation (SD) 7.46). Two studies included patients with physical health comorbidity (brucellosis and human immunodeficiency virus (HIV) (Emadi-Kouchak et al., 2016; Jafari et al., 2015).

Assessment of bias

The quality of the included clinical trials was assessed systematically via evaluation of bias in accordance with the *Cochrane Handbook for Systematic Review of Interventions* (Higgins and Green, 2011). The results are summarised in Supplementary Material, Table 1. Three studies had a high risk for bias for inadequate reporting of withdrawals and drop-outs (Abbasi et al., 2012; Magalhães et al., 2013; Müller et al., 2006). One study was found to have a high risk of bias in several categories for inadequate reporting of participant selection, concealment, control of confounders and data collection methods (Majid et al., 2015). Publication bias was assessed using a funnel plot, as shown in Supplementary Material, Figures 1 and 2. An Egger's test could not be conducted as a minimum of 10 studies is required for sufficient power of this test to distinguish chance from real asymmetry in the funnel plots.

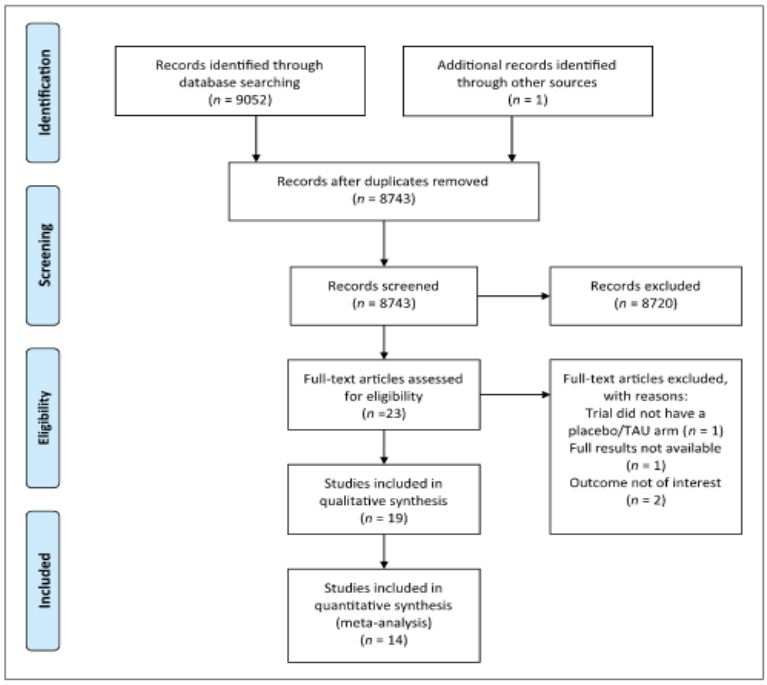

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. TAU: treatment-as-usual.

Outcomes

Anti-depressant effect of anti-inflammatory agents. With regards to the primary outcome, six trials (n=214 patients) showed lower post-treatment depressive symptoms scores following treatment with anti-inflammatory interventions when compared to TAU or placebo with an overall effect size of −0.71 (95% confidence interval (CI) −1.24 to −0.17, p=0.009; I^2= 69%, p=0.007) (Figure 2). These studies did not report change in depressive symptoms scores and only provided data on post-treatment severity, thus they are analysed separately.

Five of the 12 available studies investigating MDD and bipolar depression reported mean change in depressive symptoms scores at the end of treatment. From the results of these studies, anti-inflammatory treatment did not yield a statistically significant antidepressant effect (i.e. change in depressive symptom scores from baseline to outcome) with a pooled effect size (SMD) of −0.52 (95% CI −1.01 to 0.05, p=0.07) (Figure 3). This effect estimate was based on a total of 194 participants and was associated with substantial heterogeneity; I^2=72% (p<0.001).

Anti-manic effect of anti-inflammatory agents. Three studies investigated the effect of anti-inflammatory treatment in a total of 96 patients. Overall, anti-inflammatory treatment reduced manic symptom scores with an overall effect size of −0.72 (95% CI −1.31 to −0.13, p=0.02, I^2= 46%, p=0.16) (Figure 4). The studies included in this analysis only reported post-treatment severity and not change in manic symptoms scores.

Subgroup analyses. We conducted sub-analyses on the main comparisons in studies of sufficient size and found that of the seven studies using adjunctive NSAIDs for depressive symptoms, six were RCTs of celecoxib. Celecoxib showed a trend of superiority over placebo and/or TAU when comparing post-treatment depressive symptom scores however this was not statistically significant (four RCTs, n=109; SMD −0.81, 95% CI −1.71 to 0.09, p=0.08; I^2=79%, p=0.003). Two RCTs (Abbasi et al., 2012; Arabzadeh et al., 2015) were excluded from this subgroup analyses because they did not report post-treatment symptom severity scores.

To determine the influence of a placebo-only comparator versus placebo added to TAU we conducted a sub-analysis excluding studies that used a placebo-only control group. Only one such study was identified (Emadi-Kouchak et al., 2016), which was included in the original meta-analysis of the secondary outcome measure. The sub-analysis revealed that anti-inflammatories still

Table 1. Identified clinical trials investigating anti-inflammatory treatment in major depressive disorder.

Study number	Source	Type	No. of patients		Comorbidity	Depression diagnosis and outcome measures	Duration	Treatment and number	Results (mean, SD, total)	
			Randomised	Analysed					Treatment	Placebo
	Non-steroidal anti-inflammatory drugs (NSAIDs)									
1	Müller et al., 2006	Peer reviewed	40	18	None	DSM IV, HAM-D	6 weeks	NARI with placebo (20) vs NARI with celecoxib 400 mg OD (20)	7.9, 7.1, 10	12.1, 8.3, 8
2	Akhondzadeh et al., 2009	Peer reviewed	40	37	None	DSM IV, HAM-D≥18	6 weeks	SSRI with placebo (20) vs SSRI with celecoxib 200 mg BD (20)	Change score: −13.2, 4.26, 19	Change score: −10.2, 3.77, 18
3	Abbasi et al., 2012	Peer reviewed	40	37	None	DSM IV, HAM-D≥18	6 weeks	SSRI with placebo (20) vs SSRI with celecoxib 200 mg BD (20)	Change score: −13.4, 3.88, 19	Change score: −10.05, 3.15, 18
4	Majid et al., 2015	Peer reviewed	30	23	None	DSM IV, HAM-D 18–36	8 weeks	SSRI with placebo (15) vs SSRI with celecoxib 100 mg BD (15)	7.9, 4.0, 14	10.4, 3.0, 9
5	Jafari et al., 2015	Peer reviewed	40	40	Brucellosis	HAM-D<19	8 weeks	Antibiotic with placebo (20) vs antibiotic with celecoxib 200 mg BD (20)	9.6, 3.79, 20	16.6, 2.96, 20
	Cytokine inhibitors									
6	Raison et al., 2013	Peer reviewed	60	60	None	HAM-D	12 weeks	Three infusions at wk 0, 2 and 6 of placebo (30) vs infliximab 5 mg/kg (30)	Change score: −7.6, 7.0, 30	Change score: −9.6, 7.0, 30
	Minocycline									
7	Emadi-Kouchak et al., 2016	Peer reviewed	50	46	HIV	HAM-D<18	6 weeks	Placebo (23) vs minocycline 100 mg BD (23)	Change score: 3.83, 1.92, 23	Change score: 1.65, 2.12, 23

HAM-D: Hamilton Depression Rating Scale; SD: standard deviation; NARI: noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; DSM: diagnostic and statistical manual of mental disorders; OD: once daily; BD: twice daily.

did not yield a statistically significant antidepressant effect when considering the secondary outcome of change in depressive symptoms (four RCTs, n=148, SMD=−0.38, 95% CI −1.01 to 0.25, p= 0.24, I^2=70%, p=0.02). A sub-analysis of trials recruiting patients with bipolar depression indicated that anti-inflammatory treatments showed a trend towards an antidepressant action in this group, although this was not statistically significant (three RCTs, n=133, SMD=−0.42, 95% CI −0.88 to 0.04, p= 0.07, I^2=38%, p=0.2).

Further sub-analyses indicated that anti-inflammatory treatments had an antidepressant action when considering the primary outcome of post-treatment symptom severity (five RCTs, n=174, SMD=−0.51, 95% CI −0.81 to −0.20, p=0.001, I^2=0%, p=0.50) irrespective of the presence of a co-morbid physical health condition. However the secondary outcome measure of change in depressive symptoms from baseline to endpoint were not statistically significant when studies of patients with physical health comorbidities were excluded (four RCTs, n=148, SMD=−0.38, 95% CI −1.01 to 0.25, p=0.24, I^2=70%, p=0.02),

Meta-regression analyses were completed to determine the association of study quality, baseline symptom severity and duration of treatment with antidepressant effects of anti-inflammatory agents. None of the three variables significantly affected the SMD for the effect of anti-inflammatory agents on post-treatment depressive symptom severity. Conversely, all three variables showed a significant linear relationship for the secondary outcome of effect of anti-inflammatory agents on change in depressive symptom scores: studies with a poorer quality score (p=0.004), more severe baseline depression severity (p = 0.003) or longer duration of symptoms (p=0.005) yielded a greater anti-inflammatory treatment benefit.

Qualitative analysis

Given the variable profile of each anti-inflammatory compound, the qualitative analysis of results will be divided by agent.

Table 2. Identified clinical trials investigating anti-inflammatory treatment in bipolar disorder.

Study number	Source	Type	No. of patients		Symptoms	Outcome measures	Duration	Treatment and number	Results (mean, SD, total)	
			Randomised	Analysed					Treatment	Placebo
	Non-steroidal anti-inflammatory drugs (NSAIDs)									
8	Nery et al., 2008	Peer reviewed	32	28	BP I or II experiencing major depressive or mixed episode	DSM IV, HAM-D	6 weeks	TAU plus placebo (14) vs TAU plus celecoxib 400 mg OD (14)	10.5, 3.7, 14	10.6, 6.5, 14
9	Saroukhani et al., 2013	Peer reviewer	32	30	Stable BP I or II (YMRS≤12)	DSM IV, HAM-D YMRS	6 weeks	Lithium plus placebo (15) vs lithium plus aspirin 80 mg TDS (15)	HAMD: 9.0, 3.2, 15 YMRS: 4.8, 3.1, 15	HAMD: 9.9, 3.6, 15 YMRS: 5.3, 3.3, 15
10	Arabzadeh et al., 2015	Peer reviewer	48	46	Moderate to severe mania (YMRS≥20)	HAM-D, YMRS	6 weeks	Valproate 800 mg OD plus placebo (23) vs valproate 800 mg OD plus celecoxib 200 mg BD (23)	YMRS: 3.86, 2.54, 23 HAM-D (change score): −2.17, 2.21, 23	YMRS: 10.83, 7.52, 23 HAM-D (change score): 0.09, 2.29, 23
11	Kargar et al., 2015	Peer reviewed	35	35	Moderate to severe mania	HAM-D, YMRS	6 weeks	ECT plus placebo vs ECT plus celecoxib 200 mg BD	YMRS: 11.11, 9.45, 16	YMRS: 15.83, 13.24, 19
	N-acetyl cysteine (NAC)									
12	Berk et al., 2008	Peer reviewed	75	75	Stable BP I or II	MADRS, YMRS, Bipolar depression rating scale (BDRS)	24 weeks	TAU plus placebo (37) vs TAU plus NAC 1 g BD (38)	MADRS: 6.6, 7.4, 38 BDRS: 6.7, 6.4, 38 YMRS: 2.1, 3.3, 38	MADRS: 14.0, 11.5, 37 BDRS: 12.0, 8.8, 37 YMRS: 3.7, 5.4, 37
13	Magalhães et al., 2011b (sub group analysis of Berk et al., 2008)	Peer reviewed	14	14	BP II disorder only	MADRS, BDRS (bipolar depression rating scale)	24 weeks	TAU plus placebo (7) vs TAU plus NAC 1 g BD (7)	MADRS (change score): −7, 43, 7 BDRS (change score): −10, 26, 7	MADRS (change score): −1, 8, 7 BDRS (change score): −1, 13, 7
14	Magalhães et al., 2013 (sub group analysis of Berk et al., 2008)	Peer reviewer	15	13	BP I or II with mania or hypomania	YMRS, MADRS, BDRS	24 weeks	TAU plus placebo (7) vs TAU plus NAC 1 g BD (8)	YMRS: 1, 9, 8 MADRS: 5, 44, 8 BDRS: 8, 35, 8	YMRS: 8, 24, 7 MADRS: 27, 34, 7 BDRS: 19, 32, 7

BP: bipolar disorder; ECT: electroconvulsive therapy; MADRS: Montgomery-Asberg Depression Rating Scale; OD: once daily; SD: standard deviation; TAU: treatment-as-usual; TDS: three times daily; YMRS: Young Mania Rating Scale.

Celecoxib. We identified 11 RCTs of celecoxib in mood disorders. Six of these trials included patients with a diagnosis of MDD (Abbasi et al., 2012; Akhondzadeh et al., 2009; Jafari et al., 2015; Majid et al., 2015; Mohammadinejad et al., 2015; Müller et al., 2006).

Two studies included patients with bipolar depression (Halaris et al., 2015; Nery et al., 2008). The RCT by Nery et al. showed that patients experiencing acute bipolar depression experienced a rapid but short-lived antidepressant effect with celecoxib; this was not maintained at the study end-point (Nery et al., 2008). The other RCT was not included in our meta-analysis as full results were not available although the authors' interim analysis showed that participants receiving celecoxib as an adjunct to escitalopram had a reduction in HAM-D mean scores compared to placebo (Halaris et al., 2015).

Three RCTs have investigated celecoxib in the treatment of moderate to severe mania (Arabzadeh et al., 2015; Kargar et al., 2015; Mousavi et al., 2017). One of these studies investigated celecoxib as an add-on to sodium valproate and found a significant difference in the change in YMRS scores at the six-week endpoint compared to baseline in the two groups with an effect size of 1.16 for celecoxib (Arabzadeh et al., 2015). Another study investigated celecoxib as an adjunct to electroconvulsive therapy but did not find that the addition of celecoxib had any significant effect on

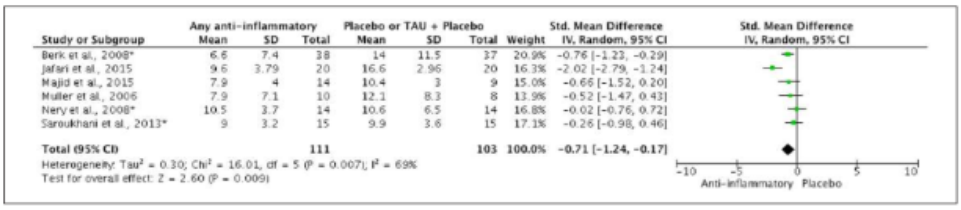

Figure 2. Depression symptoms scores (post-treatment) (pooled effect size).
*Denotes studies in bipolar disorder. 'Total' refers to number of participants (*n*); CI: confidence interval; SD: standard deviation; TAU: treatment-as-usual.

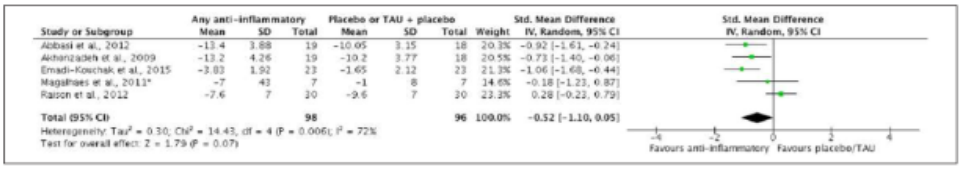

Figure 3. Change in depressive symptom scores.
*Denotes study in bipolar disorder. 'Total' refers to number of participants (*n*); CI: confidence interval; SD: standard deviation; TAU: treatment-as-usual.

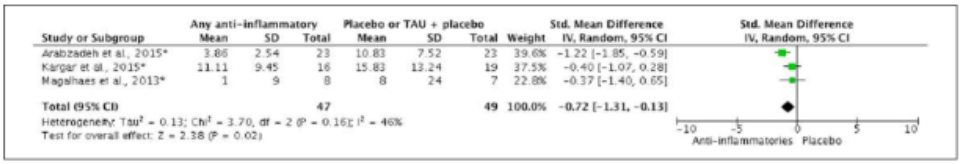

Figure 4. Manic symptoms scores (post-treatment).
*Denotes studies in bipolar disorder. 'Total' refers to number of participants (*n*); CI: confidence interval; SD: standard deviation; TAU: treatment-as-usual.

treatment response (Kargar et al., 2015). More recently Mousavi and colleagues (2017) have completed a RCT of celecoxib 200 mg daily added to lithium and risperidone in 42 adolescent patients with bipolar mania. The authors report significantly greater improvement in YMRS scores in the celecoxib group compared with the placebo group from baseline YMRS score at week 8 (p=0.04). There were no serious adverse events reported. The results from this study could not be included in our quantitative synthesis as the study remains unpublished at the time of writing and authors did not respond to our requests to access for their data.

Overall current evidence indicates that celecoxib may be associated with antidepressant effects in patients with MDD without an increased risk of adverse effects. However there are insufficient trials to assess the efficacy of celecoxib in bipolar depression or mania; larger-scale RCTs are required to support this claim.

Cytokine inhibitors. Although previous studies have investigated the effect of cytokine inhibitors on depressive symptoms in patients with physical health comorbidities, we were able to identify only one study in which examined the effect of cytokine inhibitors in primary mood disorders (Raison et al., 2013). This was an RCT investigating the TNFα antagonist, infliximab, for use in treatment-resistant depression. The authors did not find a significant difference in change in depressive symptom scores between treatment groups, but an exploratory analyses focusing on patients with a baseline C-reactive protein (CRP) concentration greater than 5 mg/L revealed a treatment response (50% reduction in HAM-D score) of 62% in infliximab-treated patients versus 33% in placebo-treated patients (Raison et al., 2013). Conversely the authors found that in patients with CRP<5mg/L, treatment response was 41% for the infliximab group and 57% for the placebo group. Thus cytokine inhibitors may have antidepressant effects in patients with high baseline inflammatory markers, although further studies are required to confirm this.

NAC. We identified six studies, all by the same research group, investigating the use of NAC. The same dose of NAC (2 g) was used in all studies. We only included three of these studies (Berk et al., 2008; Magalhães et al., 2011b, 2013) in our quantitative analysis, as others either did not report change in symptoms scores or symptom severity (Dean et al., 2012; Waterdrinker et al., 2015) or because there was incomplete reporting of results (Berk et al., 2012, 2014). The three studies included all reported separate findings of the same RCT (Berk et al., 2008): two investigated change in depressive symptoms as their primary outcome measure (Berk et al., 2008; Magalhães

et al., 2011a) and one study investigated the effect on manic symptoms (Magalhães et al., 2013). All three studies supported the use of NAC as an adjunctive treatment for both depressive and manic symptoms without any serious adverse effects reported. Study size varied from 15–75 participants and study duration was 24 weeks.

A study excluded from the current meta-analysis examined the use of NAC as a maintenance treatment for bipolar disorder (Berk et al., 2012). This study (n=149) was an eight-week open-label trial of adjunctive NAC prior to a 24-week RCT. Results showed a decrease in symptoms in the open-label phase, but no significant change in outcome measures were found between the NAC and placebo groups at the end of the RCT phase, which the authors argue could be due to a ceiling effect, with participants responding to eight weeks' treatment with NAC In the open-label phase.

The same group has also investigated the use of NAC as an adjunctive treatment for 12 weeks in 252 participants with unipolar depression (Berk et al., 2014). The authors did not find any significant difference in MADRS scores between groups at the end of the treatment phase. We were unable to include either of these studies in our analysis as the authors did not report outcomes that met our inclusion criteria, and did not respond to requests for access to full results.

In summary, the evidence from one RCT and its subsequent secondary analyses (Berk et al., 2008; Magalhães et al., 2011b, 2013) may support the hypothesis that adjunctive NAC may ameliorate depressive and possibly manic symptoms in patients with bipolar disorder. However a more recent study with a larger sample size did not find any significant improvement in symptoms following treatment with NAC in MDD (Berk et al., 2014). Further well-designed, larger controlled trials are required before NAC use can be recommended for routine clinical use in both bipolar disorder and MDD.

Aspirin. Only one RCT of aspirin use as an adjunct to lithium in the treatment of bipolar disorder was identified (Saroukhani et al., 2013). The primary outcomes in this study were symptoms of sexual (erectile) dysfunction in euthymic patients with bipolar disorder. By the end of the six-week study period, there was no significant difference in either depressive or manic symptoms scores between the treatment and control groups. Although further studies are underway investigating the use of aspirin in mood disorders (Savitz et al., 2012), at present there is insufficient evidence to support its use, although there is evidence to support the safety and tolerability of concomitant aspirin and lithium use (Saroukhani et al., 2013).

Minocycline. We were able to find only one RCT of minocycline for the treatment of depressive symptoms (Emadi-Kouchak et al., 2016). This was a six-week study of 46 patients diagnosed with HIV+, presenting with mild to moderate depressive symptoms (HAMD score≤18). Participants received minocycline monotherapy or placebo without any other pharmacological or psychological treatment for MDD. The authors found significantly greater improvements in HAMD scores in patients in the minocycline group compared to those in the placebo group. There were also more partial responders in the minocycline group compared to the placebo group. There was only one participant in the study who made a full response (≥50% reduction in HAMD score), and they were in the minocycline group. The authors did not find any significant difference in the frequency of adverse effects between groups. The only other study investigating the use of minocycline for the treatment of mood disorders that was identified is an open label study of patients with psychotic unipolar depression (Miyaoka et al., 2012). The results indicate that minocycline augmentation of antidepressant treatment was effective in improving depressive symptoms and was well tolerated. Despite a lack of further studies of minocycline for the treatment of mood disorders, our search indicated multiple studies currently underway investigating the use of minocycline for both MDD and bipolar disorder (Dean et al., 2014; Husain et al., 2015, 2016; Savitz et al., 2012). The results of these trials will add to the current evidence base for the efficacy and safety of minocycline in the treatment of mood disorder.

Adverse effects. Adverse effects from each RCT included are summarised in Table 3. Conventional NSAIDs are known to be associated with gastrointestinal (GI) side effects such as upper GI bleeding (Wolfe et al., 1999). Selective COX-2 inhibitors such as celecoxib are thought to be associated with cardiovascular adverse events such as atherosclerosis and myocardial infarction due to possible increased pro-thrombotic activity (Mukherjee et al., 2001). The tetracycline antibiotic minocycline has been associated with GI side effects, dizziness, skin pigmentation and lupus (Garner et al., 2012). None of the trials reported a serious adverse event and no incident of GI bleed or cardiovascular side effect was reported.

Trials of cytokine inhibitors did not report a significant association with increased likelihood of infections.

An RCT of NAC in depression reported that the treatment group had a significantly greater incidence of GI adverse effects compared to placebo (p=0.005). The NAC group was also more likely to experience musculoskeletal adverse effects than the placebo group (p=0.025) (Berk et al., 2014). An earlier trial of NAC in bipolar disorders by the same authors did not show any significant difference in the frequency of adverse effects between treatment and placebo groups (Berk et al., 2008).

Discussion

This meta-analysis suggests that anti-inflammatory treatments may have a beneficial effect on both depressive and manic symptoms. When assessing the primary outcome measure of post-treatment symptom severity, the quantitative analysis of six anti-inflammatory RCTs (n=214 participants with either MDD or bipolar depression) demonstrated a significant moderate antidepressant effect (SMD=−0.71). This is comparable with effect sizes reported in clinical trials of antidepressants, where an effect size of 0.40 or higher is considered a clinically significant response criterion (Faries et al., 2000). A sub-analysis of three trials in patients with bipolar depression showed that anti-inflammatory agents may have antidepressant actions in this group, although the overall effect (SMD −0.42) was not statistically significant and included substantial heterogeneity. With regards to the anti-manic effects of anti-inflammatory agents, there were only three studies of 96 patients evaluated and thus the pooled effect size of −0.72 for these studies must be treated with caution, making it impossible to base any clinical recommendations on this evidence.

Meta-regression analyses of included trials indicated that study quality, baseline symptom severity and duration of

Table 3. Adverse effects (AEs) of anti-inflammatory agents.

Non-steroidal anti-inflammatory drugs	
Müller et al., 2006	No adverse effects reported by either group
Nery et al., 2008	No significant difference in frequency of adverse effects between treatment and placebo. Two patients from the celecoxib group dropped out due to adverse events (rash). In both subjects the rash was mild, localized, and disappeared a few days following discontinuation of celecoxib.
Akhondzadeh et al., 2009	No significant difference in frequency of adverse effects between treatment and placebo
Abbasi et al., 2012	No significant difference in frequency of adverse effects between treatment and placebo
Saroukhani et al., 2013	No significant difference in frequency of adverse effects between treatment and placebo.
Halaris et al., 2014	No adverse event reported (interim analysis only)
Arabzadeh et al., 2015	No significant difference in frequency of adverse effects between treatment and placebo. No serious AE reported. No GI bleed or cardiovascular side effect in either group.
Jafari et al., 2015	No significant difference in frequency of adverse effects between treatment and placebo. No serious AE reported. No GI bleed or cardiovascular side effect in either group.
Kargar et al., 2015	No comment on adverse effects documented
Majid et al., 2015	No significant difference in frequency of adverse effects between treatment and placebo. No serious AE reported. No GI bleed or cardiovascular side effect in either group.
Cytokine inhibitors	
Raison et al., 2012	Except for an increased number of participants positive for elevated urinary leukocyte esterase in the placebo group, no statistically significant differences between groups were found. No serious adverse events were reported for either group.
N-acetyl cysteine	
Berk et al., 2008	Adverse events reported in more than 15% of the NAC group included changed energy (21% NAC, 27% placebo), headaches (18% NAC, 8% placebo), heartburn (16% NAC, 8% placebo), and increased pain in joints (16% NAC, 8% placebo). No reported event was significantly more common in the NAC group compared with the placebo group.
Magalhães et al., 2011b (sub group analysis of Berk et al., 2008)	Three participants in the NAC (sweating, thirst and headache) and three in the placebo group (palpitations, nausea and diarrhoea) reported side effects during the trial.
Magalhães et al., 2011a (sub group analysis of Berk et al., 2008)	Side effects were mild; three patients on NAC complained of headache, and two of abdominal pain and diarrhoea. One patient on placebo complained of palpitations and one of diarrhoea.
Berk et al., 2012	No comment on adverse effects documented
Magalhães et al., 2013 (sub group analysis of Berk et al., 2008)	No comment on adverse effects documented
Berk et al., 2014	There were a total of nine serious adverse events, five in the NAC group and four in the placebo group, with no significant differences in the groups observed. The NAC group had a significantly greater % of GI problems (33.9%, *n*=43) compared to placebo (18.4%, *n*=23) (p=0.005). The NAC group (3.9%, *n*=5) was more likely to have musculoskeletal complaints than the placebo group (0.00%, *n*=0) (p=0.025).
Minocycline	
Emadi-Kouchak et al., 2015	No significant difference in frequency of adverse effects between treatment and placebo. No serious AE reported.

GI: gastrointestinal; NAC: N-acetyl cysteine.

treatment with antidepressants did not influence the effect of anti-inflammatory treatments on the primary outcome measure of post-treatment symptom severity scores. However all three of these variables showed a significant linear relationship for the effect of anti-inflammatory agents on the secondary outcome of change in depressive symptom scores; there was a negative correlation between study quality and anti-inflammatory treatment effect, whereas baseline symptom severity and duration of depressive symptoms were positively correlated to a treatment effect.

Limitations

The majority of studies included in our review had small sample sizes and had only small to medium effect sizes with high heterogeneity. For the meta-analysis we were unable to pool SMDs from all studies in unipolar and bipolar depression because not all of them used the same symptom rating scales and not all of them reported post-treatment symptom severity as an outcome measure; instead they provided data on change in symptom scores. The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011) suggests only pooling change in symptoms scores with post-symptom severity measures into one mean difference analysis if the same rating scale is used in all studies. Therefore the pooled SMDs reported in this meta-analysis may not be indicative of the true effect size of anti-inflammatory agents in the treatment of bipolar and unipolar depression.

Although we found no evidence of publication bias, this was not assessed statistically due to small numbers and sizes of studies included. Furthermore, treatment durations tended to be short, mostly ranging from 6–12 weeks, meaning that we were unable to inspect the long-term adverse effects, tolerability and efficacy of anti-inflammatory treatment. Although we made efforts to summarise adverse effects of the anti-inflammatory

interventions, not all studies reported these, limiting a full evaluation of the safety and tolerability of these interventions. It is also important to note that the antidepressant effect of the interventions may be mediated via their effects on somatic comorbidities, although we have only included three studies in which patients recruited were diagnosed with somatic comorbidity. Finally, the generalizability of nine studies' findings included in this systematic review is potentially questionable since these trials were all conducted in Iran and trials in high-income countries may yield different results.

Implications and direction for future research

The current evidence for the use of anti-inflammatories as treatments for mood disorders remains inconsistent. Current studies are limited by small sample sizes, short durations, differing baseline symptomatology and poorly defined illness durations, which makes it impossible to provide recommendations on the routine clinical use of these agents in the treatment of mood disorders. The most investigated anti-inflammatory treatment is celecoxib, with many studies reporting antidepressant effects when used as an adjunct or as monotherapy (Abbasi et al., 2012; Akhondzadeh et al., 2009; Jafari et al., 2015; Majid et al., 2015; Müller et al., 2006). There are also indications that celecoxib may have anti-manic properties, although this assumption is based on a small study not evaluating long-term effects on response and remission (Arabzadeh et al., 2015). Although it has been reported that NSAIDs carry an increased risk of gastrointestinal (Wolfe et al., 1999) and cardiovascular (Mukherjee et al., 2001) adverse effects, this has not been supported by our analysis. However, it is important to note that three studies did not provide any comment on adverse effects (Berk et al., 2012; Kargar et al., 2015; Magalhães et al., 2013). Furthermore, given the short study period for many of the trials, it is possible that adverse effects were not identified in the study timeframe. Given these important caveats we would suggest that it is important to proceed cautiously before implementing celecoxib in routine clinical practice, and the potential therapeutic benefits in mood disorder must be balanced against the risk of adverse effects. More large-scale clinical trials of celecoxib for patients with depression (both unipolar and bipolar) and mania are warranted. Such trials will assess longer-term safety and tolerability as well as effects on response and remission rates in both MDD and bipolar disorder.

Given the small number of studies that have investigated cytokine inhibitors, NAC and minocycline for the treatment of mood disorders, we would encourage further high-quality controlled clinical trials to contribute to the current body of evidence. More studies are required, particularly investigating whether these anti-inflammatory drugs are effective in the treatment of mania.

Numerous mechanisms have been proposed to explain the association between inflammation and mood disorders, ranging from disturbed neurotransmission, to disturbances in the biological mediators of stress (i.e. cortisol levels) and the release of neurotoxic metabolites. It is possible that anti-inflammatory agents act on several of these mechanisms to produce an antidepressant and possibly an antimanic effect. Biological mediators of stress (e.g. glucocorticoids) and peripheral inflammation have been found to activate neuroinflammatory processes, which could lead to the onset of mood symptoms (Miller and Raison, 2016). In particular, the kynurenine pathway is an inflammatory pathway that is believed to be involved in mood disorders, and has shown to be modulated by anti-inflammatory agents. Pro-inflammatory cytokines can activate the enzyme indoleamine 2,3-dioxygenase (IDO). Increased IDO activity decreases synthesis of serotonin from tryptophan, leading to the production of pro-depressant and neurotoxic metabolites (Grosse et al., 2016). Anti-inflammatories have been shown to block pro-inflammatory cytokines, which activate IDO.

We would suggest that future treatment trials should also include the measurement of biomarkers in order to identify whether the clinical benefits of anti-inflammatory medications occur alongside a change in inflammatory activity, or in only a biological subgroup of patients experiencing a mood disorder. Studies have already found that patients with both depression and bipolar disorder may have abnormal levels of circulating inflammatory markers (Dowlati et al., 2010; Goldstein et al., 2009; Howren et al., 2009). A recent meta-analysis has found that in MDD, these levels may normalise with treatment and the authors identified TNFα as a potential marker for treatment-resistant depression (Strawbridge et al., 2015). However, plasma cytokines are strongly affected by environmental factors (e.g. age, gender, exercise, obesity, insulin resistance, smoking), and by the heterogeneity of mood disorder itself, and so exhibit high inter-individual variance. Instead it has been suggested that measuring the pro-inflammatory state of monocytes, the main cytokine producers, via gene expression may be a more sensitive way to detect inflammation (Carvalho et al., 2014; Grosse et al., 2015). Future RCTs of anti-inflammatory medications should attempt to incorporate these putative biomarkers in order to determine whether the mechanism of any antidepressant action is due to the inhibition of inflammatory processes. The results of such studies may provide clinicians with clear guidelines on when to implement anti-inflammatory treatment for patients with treatment-resistant symptoms.

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Chapter 5: Published pilot randomised controlled trial

Original Paper

Minocycline as an adjunct for treatment-resistant depressive symptoms: A pilot randomised placebo-controlled trial

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Abstract

Background: Evidence suggests that anti-inflammatory medication may be effective in the treatment of depressive symptoms. In this study, we aimed to investigate whether minocycline added to treatment as usual (TAU) for 3 months in patients with treatment-resistant depression will lead to an improvement in depressive symptoms.

Methods: Multi-site, 12-week, double-blind, placebo-controlled, pilot trial of minocycline added to TAU for patients suffering from DSM-5 major depressive disorder, whose current episode has failed to respond to at least two antidepressants. The primary outcome measure was mean change in Hamilton Depression Rating Scale (HAMD-17) scores from baseline to week 12. Secondary measures were the Clinical Global Impression scale (CGI), Patient Health Questionnaire-9 (PHQ-9), the Generalised Anxiety Disorder scale (GAD-7) and EuroQoL (EQ-5D) quality-of-life questionnaire. Side-effect checklists were also used. Minocycline was started at 100 mg once daily (OD) and increased to 200 mg after 2 weeks.

Results: A total of 41 participants were randomised, with 21 in the minocycline group and 20 in the placebo group. A large decrease in HAMD scores was observed in the minocycline group compared to the placebo group (standardised effect size (ES) −1.21, $p < 0.001$). CGI scores in the minocycline group also showed a large improvement compared with placebo (odds ratio (OR): 17.6, $p < 0.001$). PHQ-9, GAD-7 and EQ-5D total showed more moderate improvements (ES – 0.4–0.5).

Conclusion: The findings indicate that adjunctive minocycline leads to improvement in symptoms of treatment-resistant depression. However, our findings require replication in a larger sample.

Trial Registration: ClinicalTrials.gov identifier: NCT02263872, registered October 2014.

Keywords
Inflammation, depression, minocycline

Introduction

Depression is the leading cause of disability worldwide (World Health Organisation, 2017). Although depressive symptoms are amenable to antidepressant treatments, a high proportion of patients neither responds adequately nor achieves remission (Rush et al., 2006). For example, in the Sequenced Treatment Alternatives for the Relief of Depression (STAR*D) study, the response and remission rates with stage 1 treatment (citalopram) were 49% and 37%, respectively. The additional response rates decreased to 16% and 13%, respectively, over the subsequent next three treatment steps (Rush et al., 2006). A recent meta-analysis of current pharmacological treatments for depressive disorder in primary care showed only a relatively small effect size for antidepressant treatments when compared with placebo (Linde et al., 2015). Thus, there remains a clear need for more efficacious and novel treatment approaches.

Recently, there have been promising preclinical and clinical data implicating inflammatory processes in a range of psychiatric disorders including depression. The findings include: a meta-analysis showing that pro-inflammatory cytokines are increased in the blood of patients with major depressive disorder (O'Donovan et al., 2013); and that peripheral administration of a pro-inflammatory cytokine (IFN-α) induces a depressive syndrome in many patients receiving it as a treatment for hepatitis (Van Gool et al., 2003). Treatment with cytokine IFN-α corresponded with the development of depressive symptoms in up to 45% of patients with no previous history of depression (Capuron and Miller, 2011). Longitudinal studies have demonstrated that high plasma pro-inflammatory protein levels precede, and thus potentially cause depressive symptoms (Gimeno et al., 2009; Khandaker et al., 2014). The most convincing evidence for a close relationship between inflammation and depression is the

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very frequent comorbidity of depressive symptoms with virtually all chronic inflammatory or autoimmune disorders (Capuron and Miller, 2011). Large proportions (probably >50%) of patients with rheumatoid arthritis and systemic lupus erythematosus have depressive or other psychiatric symptoms. Inflammatory medical illnesses, both CNS and peripheral, are associated with greater rates of depression and in patients with Crohn's disease and comorbid depression, bouts of physical disease activity tend to co-occur with depressive episodes (Mardini et al., 2004). Although less robust, evidence also suggests that inflammation when present is associated with more severe course of illness (Zalli et al., 2016), and more prominent in people who are resistant to monoaminergic drugs (Carvalho et al., 2013; Grosse et al., 2016). There is also some preliminary evidence that anti-cytokine treatment may have antidepressant properties (Kappelmann et al., 2016).

Current evidence suggests that the addition of an anti-inflammatory medication may be effective in the treatment of depressive illness. Muller et al. were the first to demonstrate a reduction in depressive symptoms when using celecoxib, a COX-2 selective non-steroidal anti-inflammatory drug, in addition to reboxetine for the treatment of major depressive disorder in a double-blind, randomised, placebo-controlled pilot study (Muller et al., 2006). A recent meta-analysis showed that augmentation with celecoxib is an effective add-on treatment for unipolar depressive patients (Faridhosseini et al., 2014). However, other studies have found that anti-inflammatories may have an antagonistic effect on the antidepressant actions of selective serotonin reuptake inhibitors (SSRIs) (Warner-Schmidt et al., 2011). Further work is needed in this area to clarify the role of inflammatory processes and anti-inflammatories in the treatment of depression.

The tetracycline antibiotic minocycline has been proposed for the treatment of depressive symptoms, as well as negative symptoms in schizophrenia (Chaudhry et al., 2012; Soczynska et al., 2012). Studies in animal models have shown that minocycline may induce antidepressant-like effects (Arakawa et al., 2012). Preliminary data from an open-label study of patients with psychotic unipolar depression suggested that minocycline augmentation of antidepressant treatment was effective and well tolerated (Miyaoka et al., 2012). Minocycline has many actions on a variety of systems implicated in depression, including anti-inflammatory, anti-oxidant, anti-apoptotic, and modulation of glutamate and monoamine neurotransmission (Hashimoto and Ishima, 2010; Soczynska et al., 2012). Despite these properties, there have been no published controlled clinical trials investigating the antidepressant effects of minocycline in individuals with treatment-resistant depression.

In this double blind, randomised, placebo-controlled pilot trial, we examined the efficacy of minocycline as an adjunct to treatment as usual (TAU) for 12 weeks in patients with treatment-resistant major depressive disorder. The inflammatory hypothesis of depression predicts that minocycline augmentation should lead to an improvement in depressive symptoms in the experimental group in comparison with the control group.

Methods and materials

Overview

This was a multi-site, 12-week, double blind, placebo-controlled, pilot trial of minocycline added to TAU for patients suffering from a DSM-5 major depressive episode that has failed to respond to at least two antidepressant treatments. The study was conducted in Karachi, Pakistan, and participants were recruited from outpatient psychiatric clinics at Abbasi Shaheed Hospital, Karwan-e-Hayat Hospital, Civil Hospital, and the Institute of Behavioural Sciences between October 2014 and March 2016.

All patients provided written informed consent after reading the information provided. TAU comprised medications including antidepressants (selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, noradrenergic and specific serotonin antagonists and serotonin noradrenaline reuptake inhibitors), mood stabilisers (with the exception of valproic acid) and antipsychotics, as well as psychotherapy and other psychosocial interventions.

The trial was registered with Clinicaltrials.gov in October 2014 (ClinicalTrials.gov identifier: NCT02263872).

Randomisation and masking

An independent statistician, unknown to study personnel, randomised participants using a web-based randomisation tool (allocation ratio 1:1) to receive either minocycline or placebo, in addition to TAU. There was no further stratification. The randomisation lists were held by a pharmacist who was not involved in the research project.

Tablets were dispensed by a single pharmacy and patients, their families, referring psychiatrists, the study statistician and the research assistants carrying out the assessments were blind to the study drug until the completion of the study. Reign Nutro Pharma and Jawed Traders (Pakistan) provided minocycline and placebo in identical tablet form, matched for shape, size, texture, colour and odour. Both companies hold International Organisation for Standardisation (ISO) certification.

Sample size

A total of 41 participants were recruited and randomised into two arms.

Power calculation

This was a pilot trial and so the main objective was to estimate effect sizes. The US Food and Drug Administration guidance on drug study design recommends that a minimum of 12 subjects per group is sufficient for pilot trials (US Food and Drug Administration, 2016). In the proposed study, we aimed to recruit 20 to each treatment group: minocycline and TAU. Assuming 20% loss to follow up, with an alpha of 5% for a two-tailed test, our trial had 0.8 power to detect an effect size (ES) of 1 for a differential reduction of Hamilton Depression scores (HAMD) (Hamilton, 1960) between minocycline and TAU.

Local research ethics committee approval

Approval was obtained from the ethics committee of the Karachi Medical and Dental College and Dow University of Health Sciences, Pakistan.

Inclusion criteria

Inclusion criteria were: (1) patients aged 18 to 65 years; (2) Current Diagnostic and Statistical Manual-5 (DSM-5) diagnosis

of major depressive disorder; (3) capacity sufficient for consent to participate; (4) taking the current antidepressant medication for a minimum of 4 weeks (6 weeks for fluoxetine) prior to baseline; (5) the current episode of depression has failed to remit with at least two courses of antidepressant treatment (one of which is the current medication) at the adequate dose (according to British National Formulary and Maudsley Prescribing Guidelines); relapse while taking an antidepressant is also considered a treatment failure; (6) able to take oral medication and (7) if female, willing to use adequate contraceptive precautions and to have monthly pregnancy tests.

Exclusion criteria

Exclusion criteria were: (1) relevant medical illness (renal, hepatic, cardiac, serious dermatological disorders such as exfoliative dermatitis, systemic lupus erythematosus); (2) prior history of intolerance to any of the tetracyclines; (3) concomitant penicillin therapy; (4) concomitant anticoagulant therapy; (5) presence of a seizure disorder; (6) currently taking valproic acid; (7) any change of psychotropic medications within the previous 4 weeks; (8) diagnosis of substance-use disorder (except nicotine or caffeine) or dependence within the last 3 months according to DSM-5 criteria; (9) pregnant or breast-feeding or (10) presence of primary psychotic disorder.

The criteria for leaving the trial were: (1) patient's request; (2) at the discretion of the responsible medical officer or investigator (for example, an adverse event or poor compliance) and (3) pregnancy.

Study procedure

Recruitment. In the first instance, the research clinician approached the clinical teams to inform them about the research study and the inclusion and exclusion criteria. If patients met the entry criteria, were clinically stable and the clinical team agreed that the patient could be a possible participant, they introduced the study to the patient. With the patient's agreement, the research clinician then visited the patient to explain the research study verbally (in either Urdu or English) and to provide them with the participant information sheet (Urdu/English). The study was described to each potential participant with a witness (usually a caregiver) present. The patient had time to read and understand the patient information sheet (at least 24 hours). If they agreed to take part, a meeting (visit one) was set up with the patient in order to obtain signed informed consent for the study and also signed consent for the research team to have access to their medical notes. Literate participants signed the consent forms but, if the participant could not write their name, they placed a thumbprint on the consent form which was countersigned by the witness.

Screening visit

Confirmation of patient suitability was carried out at this point. Participants recruited to the trial underwent structured diagnostic interviews using the Mini International Neuropsychiatric Interview (MINI) to confirm a diagnosis of DSM-5 major depressive disorder (Sheehan et al., 1998). This tool has been validated for use in the local Urdu language and has been used in previous studies in Pakistan (Nisar et al., 2004). The Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) was used to measure severity and response and has also been used previously in Pakistan (Husain et al., 2014). Other inclusion/exclusion criteria were checked at this visit and confirmation of consent and pregnancy testing, if appropriate was carried out.

Follow up

Participants were randomised to receive minocycline or placebo added to TAU. Patients continued with their current treatment as prescribed by their psychiatrists. In order to keep the study design pragmatic and to test the efficacy of minocycline in routine clinical settings, participants were permitted to change medications during the study period if required. Minocycline added to TAU started at a dose of 100 mg daily and was increased after 2 weeks to 200 mg daily, taken as a single dose to encourage compliance.

The patients' day-to-day care remained the responsibility of their usual consultant psychiatrist or other mental health professional. Research assistants maintained contact throughout the study in order to respond to any concerns or changes in circumstances or mental or physical health. Contacts were twice weekly for the duration of the study. Any study-related safety concerns were the responsibility of the co-investigators who could be contacted at any time through the research team.

Outcome measures

The primary clinical outcome measure was mean change from baseline to week 12 on the Hamilton Depression Scale scores (Hamilton, 1960). Response was defined as a reduction of 50% or more of the HAMD-17. Remission was defined as a score of ≤7 of the HAMD-17.

Ratings were made on the basis of a clinical interview using HAMD-17 at baseline, weeks 2, 4, 8 and 12.

The secondary clinical outcome measures were the Clinical Global Impression (CGI) scale, a 7-point overall measure of severity (Busner and Targum, 2007); the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) a self-rated depression severity measure; the GAD-7 (Spitzer et al., 2006), a measure of generalised anxiety disorder, and the EuroQoL (EQ-5D) scale, a measure of health-related quality of life (Brooks, 1996). All assessment scales were translated for use in Urdu and have been used in previous clinical trials in Pakistan (Husain et al., 2014). Adverse effects were monitored using a rating scale that has been specifically designed for minocycline. This rating scale has been used by the authors in previous studies (Chaudhry et al., 2012).

Biomarkers

Participants were asked to provide two blood samples for research analysis. The provision of blood samples was optional and did not affect participation in the trial. These samples were collected at baseline and at week 12 and were collected to investigate the relationship of minocycline to inflammatory markers and if this relates to the subjective experience of symptom change. The biomarkers tested included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The selection of biomarkers was based on previous research that

confirms the pro-inflammatory properties of these measures (Cameron and Kelvin, 2000). CRP was used as a direct marker of inflammation. Given the funding constraints for this pilot study, we were not able to measure levels of other inflammatory biomarkers (e.g. cytokines).

Research assistant training and inter-rater reliability

Although data on inter-rater reliability was not formally collected, all assessments were carried out by research assistants who are experienced Masters' level clinical psychologists that were trained in clinical assessments and diagnostic interviews by two authors (IBC and NH).

Statistical analysis

The focus of this study was to estimate to ESs and 95% confidence intervals for treatment outcomes. All randomised participants were included in the analysis according to their treatment allocations at randomisation, according to the intention-to-treat (ITT) principle. All continuous measures, including the primary outcome HAMD were analysed with linear mixed models to account for the dependencies in the data from the repeated measures. CGI was an ordinal outcome and so a generalised linear mixed model (proportional odds) was used for this outcome. Hypotheses were two sided and tested at the $p < 0.05$ level. Standardised ESs for the treatment contrast were derived by dividing the group difference by the pooled standard deviation of the outcome scores.

Explanatory variables in the model were baseline outcome scores, treatment contrast (minocycline or placebo), time and interactions between time and treatment to allow treatment estimates to differ at 2, 4, 8 and 12 weeks. The primary outcome was mean group difference in HAMD scores at 12 weeks. The time point of interest for secondary outcomes was also 12 weeks. To deal with missing outcome data, we used the maximum likelihood (ML) approach: the main analysis used mixed effects models fit, using such models allow all available data to be included in the analysis, under the assumption that data is missing at random (MAR), that is, conditional on baseline predictors of missingness of outcomes being included in the model. To identify the latter, a binary indicator of missingness was generated for 12-week HAMD scores and predictors of missingness were sought using logistic regression and Fisher's exact test. A criterion of $p < 0.05$ was used as with the small sample there is a risk of overfitting. There was a strong association between socio-economic status and missingness, $p = 0.003$, but no other predictors of missingness. Socio-economic status was therefore included in all the primary analysis models.

For the blood markers, there were further missing data for both baseline and 12-week outcomes. Analysis was descriptive and limited to calculating ES for impact of minocycline on inflammatory marker levels, and correlations between change in inflammatory markers and HAMD scores. Given the small number of observations, robust correlation coefficients and confidence intervals were calculated as appropriate. R 3.3 and STATA v14 IC (Stata corp., College Station, TX, USA) were used to perform the analysis.

Results

Initially, 87 potential study candidates were identified. However, 30 patients did not meet study inclusion criteria and 16 chose not to take part. Therefore, 41 participants were randomised, with 21 in the minocycline group and 20 in the placebo group (see Figure 1). No significant differences were identified in baseline demographic data, including age and sex between groups (see Table 1). A total of 34 participants completed the trial.

During the course of the 12-week trial, changes to TAU were made to patients in both the minocycline and placebo groups. Five participants in the minocycline group and seven participants in the placebo group were started on an augmentation treatment (i.e. an atypical antipsychotic or benzodiazepine). One participant in the minocycline group switched their antidepressant (from one SSRI to another), and one participant in the placebo group switched antidepressants (from a SSRI to mirtazapine).

Table 2 shows descriptive statistics (mean and standard deviation (SD)) for the clinical outcome measures at baseline and 12 weeks, together with the change from baseline. Table 3 shows the parameter estimates for the generalised linear mixed model analysis, giving the baseline-adjusted mean difference between treatment groups at 12 weeks, together with the standardised regression coefficient. A strong association between treatment group and HAMD depressive symptoms at 12 weeks (ES = −1.21, $p < 0.001$) was observed in the minocycline group compared with the placebo group. The course of the HAMD scores is shown in Figure 2, with treatment differences appearing at week 4 and no overall change in the placebo group. According to the HAMD definitions of treatment response (response > 50%), 63% of the minocycline group responded to treatment compared with 22% of the placebo group (OR: 5.5, p = 0.035). There were also a greater proportion of participants that showed remission (HAMD < 7) in the minocycline group versus the placebo group (odds ratio (OR) 7.3, $p = 0.078$). Similarly, the minocycline group showed a strong response in terms of CGI relative to placebo (OR: 17.6, $p < 0.001$). In addition, the minocycline group showed greater improvement in PHQ-9 scores, GAD-7 and EQ-5D total and visual analogue scores (VAS) although the ESs in these cases were more moderate (~0.4–0.5, see Table 3).

With regards to inflammatory biomarker results, several participants refused to consent to the provision of blood samples. Baseline biomarker levels were only available for a sub-sample of approximately 17 participants (see Table 4) and we present a descriptive analysis of HAMD means in subgroups defined by CRP > 5. Only six patients had CRP levels less than 5 (two in minocycline and four in placebo). For the subgroup with CRP > 5, group difference was 17.6 (minocycline – HAMD = 15.7, placebo – HAMD = 33.3) and for CRP ≤ 5, the group difference was 1.8 points lower at 15.8 (minocycline – HAMD = 10.5, placebo – HAMD = 26.3).

There was no significant difference in the frequency of reported adverse effects between groups. Table 5 summarises all side effects reported by participants.

Discussion

To our knowledge, this is the first randomised control trial (RCT) of minocycline in patients with treatment-resistant depressive symptoms. Our findings show that minocycline may be effective as an

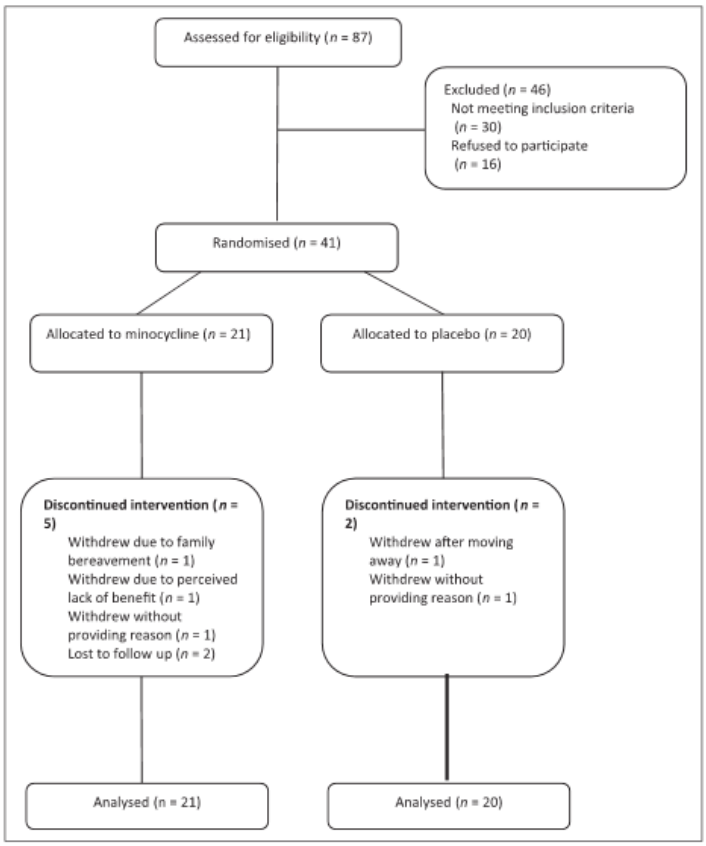

Figure 1. CONSORT flow diagram.
p values for mean group differences by week (week 2: $p = 0.73$, week 4: $p = 0.06$, week 8: $p < 0.001$, week 12: $p < 0.001$).

adjunct to TAU in patients with treatment-resistant depressive symptoms. The majority of participants in both the minocycline and placebo groups were receiving a SSRI antidepressant as part of their usual treatment. Most participants were also using an augmenting agent (either a second antidepressant or an antipsychotic). The duration since starting their first treatment for depression was over 1year for the majority of participants, which suggests that their symptoms were indeed significantly treatment refractory.

Participants randomised to minocycline showed a significant response, and the estimated mean reduction in HAMD scores was 18 points. The standardised effect size of 1.21 is large; an effect size of 0.40 or higher is considered a clinically significant response criterion in previous clinical trials of antidepressant treatments (Faries et al., 2000). The intervention was also well tolerated in comparison with placebo and there was no significant difference between groups in terms of frequency of adverse events. The absence of a response as measured by HAMD scores in the placebo group may reflect the chronicity and initial severity of the sample. A total of 95% of the participants receiving either treatment had been receiving treatment for major depressive disorder for at least 12 months. Studies have indicated that the natural history of illness and specifically, longer duration of current illness can reduce the placebo response (Rutherford and Roose, 2013). Secondly, it has been found that placebo response decreases with increasing severity of baseline depression scores, with a recent study finding that placebo response significantly declined as baseline HAMD increased (particularly as it exceeded a score of 25) (Fournier et al., 2010). The mean baseline HAMD score in the placebo group in the current study was 32.6, with only three participants scoring less than 25. It is worth noting that participants in the placebo group did show a response on the patient-rated PHQ-9 measure but not on the clinician-rated HAMD-17 and CGI measures. Lack of correlation between clinician and

patient-rated outcomes are not uncommon and previous larger trials of antidepressant treatments have also reported similar discrepancies (Targum et al., 2013). The reasons for the discrepancy in the current study are unclear, although participant motivation to be involved in the trial, a heightened awareness of symptoms at baseline, and the experimental environment itself (i.e. expectancy biases) may have affected the patients' perception of depressive symptoms and influenced self-rating during the study.

Our findings add to the growing evidence that minocycline may have antidepressant properties. As mentioned previously, open-label studies of minocycline augmentation for unipolar depression have supported this claim (Miyaoka et al., 2012). A more recent RCT of minocycline monotherapy in patients with an HIV diagnosis and mild-to-moderate depression (HAMD < 18) found significantly greater improvements in HAMD scores in patients in the minocycline group compared with those in the placebo group. There were also more partial responders in the minocycline group compared with the placebo group (Emadi-Kouchak et al., 2016). Minocycline has already shown to have beneficial effects in schizophrenia, particularly in the treatment of negative symptoms (Chaudhry et al., 2012, Oya et al., 2014). The effects of minocycline in depression may indicate that similar pathogenic mechanisms play a role in schizophrenia and in mood disorders.

Numerous mechanisms have been proposed to explain the association between inflammation and depression, ranging from disturbed neurotransmission, to disturbances in the biological mediators of stress (i.e. cortisol levels) and the release of neurotoxic metabolites. We hypothesise that minocycline acts on several of these mechanisms to produce an antidepressant effect. Biological mediators of stress (e.g. glucocorticoids) and peripheral inflammation have been found to activate neuroinflammatory processes, of which microglia exert a central role (Frank et al., 2015). Minocycline is an inhibitor of microglial activation (Soczynska et al., 2012) and has been shown to decrease depressive and anxiety symptoms in mice whist reducing pro-inflammatory cytokines (i.e. tumour necrosis factor (TNF) and interleukin (IL)-1B) and glucocorticoids (Majidi et al., 2016). The kynurenine pathway is another inflammatory pathway that is believed to be involved in depression, and has shown to be modulated by minocycline. Pro-inflammatory cytokines can activate the enzyme indoleamine 2,3-dioxygenase (IDO). Increased IDO activity decreases synthesis of serotonin from tryptophan, leading to the production of pro-depressant and neurotoxic

Table 1. Demographic characteristics of participants.

	Placebo (n = 20)	Minocycline (n = 21)
Age: median (IQR)	35 (30.5–39)	40 (30–46)
Gender		
Male: n (%)	9 (45)	11 (55)
Marital status		
Married: n (%)	13 (65)	17 (81)
Separated/widowed/single: n (%)	7 (35)	4 (19)
Socio-economic status		
Low: n (%)	19 (95)	16 (76)
Lower-middle: n (%)	0 (0)	4 (19)
Middle: n (%)	1 (5)	1 (5)
Education		
No formal education	9 (45)	10 (47.6)
Below primary (less than 5 years)	1 (5)	1 (4.8)
5 to 10 years of education	9 (45)	7(33.3)
More than 10 years of education	1 (5)	3 (14.3)
Employment		
Not employed: n (%)	11 (55)	13 (62)
Employed: n (%)	9 (45)	8 (38)
Concurrent medication		
SSRI: n (%)	18(90)	21 (100)
≥2 antidepressants: n (%)	6 (30)	9 (45)
Antipsychotic: n (%)	10 (50)	8 (38)
Benzodiazepine: n (%)	12 (60)	12 (57)
Duration since starting first treatment		
≤6 months (%)	0 (0)	1 (5)
6 to 12 months (%)	1 (5)	2 (10)
≥12 months (%)	19 (95)	18 (86)

IQR: inter-quartile range; SSRI: selective serotonin reuptake inhibitor.

Table 2. Descriptive statistics: mean clinical outcome measures (with SD) at baseline and 12 weeks with change scores for placebo and minocycline groups.

		Baseline		12 weeks		Change	
		n	Estimate	n	Estimate	n	Estimate
HAM-D: mean (SD)	Placebo	20	32.6 (10.1)	18	32.0 (11.8)	18	−0.2 (16.1)
	Minocycline	21	34.5 (10.9)	16	15.1 (13.2)	16	−18.3 (16.4)
CGI: median (IQR)	Placebo	20	5 (5, 6)	18	5 (4, 5)	18	0 (−1, 0)
	Minocycline	21	5 (5, 6)	16	3 (3, 4)	16	−2 (−2, −1)
PHQ-9: mean (SD)	Placebo	20	17.9 (5.3)	18	12.7 (5.1)	18	−5.2 (7.4)
	Minocycline	21	16.1 (5.8)	16	10.1 (5.0)	16	−7.3 (5.4)
GAD-7: mean (SD)	Placebo	20	9.7 (4.0)	18	6.2 (4.3)	18	−3.9 (5.8)
	Minocycline	21	10.3 (3·5)	16	4.7 (3.9)	16	−6 (4.1)
EQ-5D Total: mean (SD)	Placebo	20	10.1 (1.9)	18	9.2 (2.0)	18	−0.78 (2.6)
	Minocycline	21	10.1 (2.1)	16	8.1 (2.1)	16	−2.3 (2.5)
EQ-5D VAS: mean (SD)	Placebo	20	44 (19.1)	18	61.4 (15.3)	18	18.1 (26.0)
	Minocycline	21	42.4 (16.7)	16	62.8 (12.9)	16	20.9 (22.8)

HAM-D: Hamilton Rating Scale for Depression; CGI: Clinical Global Improvement; PHQ: Patient Health Questionnaire; GAD-7: Generalised Anxiety Disorder Questionnaire; EQ-5D: EuroQol-5 dimensions; Total and Visual Analogue Scale; SD: standard deviation; IQR: inter-quartile range.

Table 3. Inferential statistics for mean treatment group differences at 12 weeks adjusted for baseline outcome scores and time (weeks 2, 4 and 8) together with standardised effect size (standardised by the outcome score standard deviation).

	Group mean difference β[a] (95% CI)	Standardised effect size	Test statistic and *p* value
Clinical Outcomes			
HAM-D	−18.1 (−24.7, −11.5)	−1.21[‡]	$z = -5.36$ $p < 0.001$
PHQ-9	−2.23 (−5.38, 0.91)	−0.43	$z = -1.39$ $p = 0.163$
GAD-7	−1.93 (−4.37, 0.52)	−0.46	$z = -1.55$ $p = 0.122$
EQ-5D Total (UK)	−0.99 (−2.16, 0.18)	−0.48	$z = -1.65$ $p = 0{\cdot}098$
EQ-5D VAS (UK)	1.44 (−8.7, 11.6)	0.1	$z = 0.28$ $p = 0.780$
	Odds ratio[a] (95% CI)		
CGI	17.6 (3.91, 78.8)	N/A	$z = -3.74$ $p < 0.001$

HAM-D: Hamilton Rating Scale for Depression, PHQ: Patient Health Questionnaire, GAD: Generalised Anxiety Disorder, CGI: Clinical Global Improvement, EQ-5D: EuroQol-5 dimensions; Total and Visual Analogue Scale; CI: confidence interval; N/A: not applicable.
[a]For CGI – odds of being in a lower CGI rating category for minocycline vs placebo.

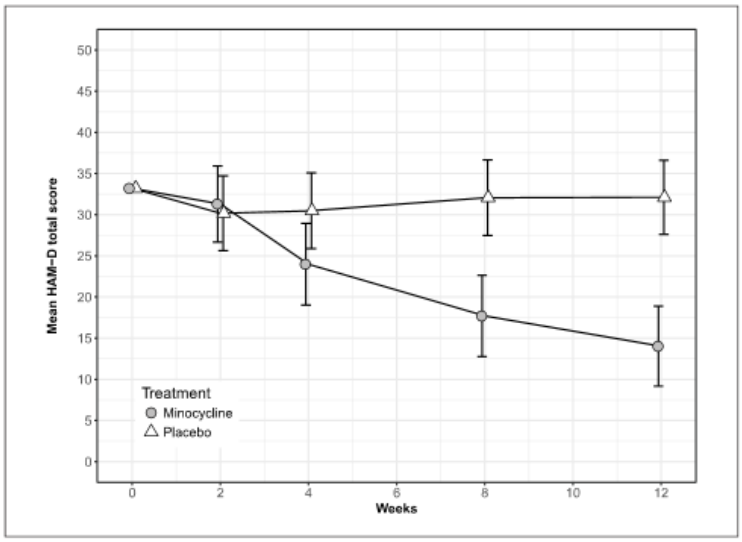

Figure 2. Predicted means and 95% confidence intervals for Hamilton Rating Scale total scores by treatment group and week for lower socio-economic status class participants (most frequent class).

Table 4. Descriptive statistics for blood inflammatory markers at baseline and 12 weeks for minocycline and placebo.

		Minocycline baseline (n = 9) 12 Weeks (n = 9)	Placebo baseline (n = 11) 12 Weeks (n = 8)	Group difference
ESR: mean (SD)	Baseline	20.6 (13.8)	20.9 (12.9)	
	12 weeks	15.8 (11.8)	26.6 (16.2)	
	Change	−4.8 (13.3)	5.7 (10.9)	−10.5 (13.1)
CRP: median (IQR)	Baseline	6 (6, 6)	6 (5, 6)	
	12 weeks	5 (5, 5)	5 (5, 6)	
	Change	−1 (−1, 0)	0 (−1, 1)	−1

ESR: erythrocyte sedimentation rate; SD: standard deviation; CRP: C-reactive protein; IQR: inter-quartile range.

Table 5. Frequency of adverse effects.

Side Effects	Minocycline n (%)	Placebo n (%)
Abdominal pain	3 (14.3)	1 (5)
Asthenia: a general feeling of weakness	4 (19)	0 (0)
Dyspepsia: indigestion	3 (14.3)	6 (30)
Fast/irregular heartbeat	1 (4.8)	1 (5)
Flatulence: abdominal gas problem	3 (14.3)	5 (25)
Headache	2 (9.5)	0 (0)
Insomnia	0 (0)	1 (5)
Myalgia: muscle pain, tenderness, or weakness	4 (19)	4 (20)
Swelling of the hands, legs, or feet	0 (0)	1 (5)
Upper respiratory infections	1 (4.8)	1 (5)

metabolites (Grosse et al., 2016). In animal models, minocycline has been shown to block the pro-inflammatory cytokine TNFα, which activates IDO (Liu et al., 2015; O'Connor et al., 2009).

Although an altered inflammatory status may underlie a subgroup of depressive disorders, recent evidence indicates that inflammatory changes with pharmacological treatment may differ, based on clinical outcome. For instance, IL-6 appears to reduce with treatment, while TNFα may reduce alongside treatment in people who show a good clinical response but remain elevated in non-responders (Strawbridge et al., 2015). This is supported by a trial identifying a greater level of clinical response to infliximab (a TNFα antagonist) in depressed patients with high levels of TNFα (Raison et al., 2013).

In the current study, we attempted to measure ESR and CRP levels at baseline and at the end of treatment, however, many participants refused to consent to the provision of blood samples. We have included analysis of the biomarker data but given the small sample size and amount of missing data, drawing further inference would be unwise. The missing data are due in part to the limited funding for the study, which did not allow for assertive follow up of participants to ensure bloods were drawn at both baseline and end-point. We will try and address this in the replication study, which we hope will have more substantial funding. Future studies of minocycline should also include measurement of inflammatory cytokines such as IL-6 and TNFα, amongst others, to determine the association between changes in inflammatory biomarkers and improvement in depressive symptoms.

Another important consideration when examining minocycline's putative antidepressant action is its pharmacokinetic properties and possible interactions with antidepressant drugs. There are limited data on the metabolism of minocycline (Nelis and De Leenheer, 1982) but it is plausible that it is mediated by cytochrome P450 enzymes, which are involved in the metabolism of many commonly used antidepressants. Further, recent in vitro studies indicate that minocycline may exert local inhibition of cytochrome p450 enzyme activity in neuronal cells (Regen et al., 2016). If minocycline does inhibit one or more cytochrome p450 enzymes either by competition for metabolism or a direct mechanistic effect, it may also be contributing to enhanced antidepressant activity by increasing the plasma or local concentration of antidepressant drugs.

The results of our study indicate that minocycline has a potential role as an augmentation strategy in patients with treatment-resistant depression. It is a readily available, inexpensive, off-patent drug that has low propensity to produce antibiotic resistance (Soczynska et al., 2012). It could be a cost-effective treatment option, particularly in settings with diminishing resources, such as low- and middle-income countries and other state-funded healthcare services. However, our findings should be interpreted in the light of certain limitations before minocycline can be recommended for routine clinical use. Firstly, as participants were followed up for a relatively short period of time, we are unable to comment on the long-term efficacy and safety of minocycline. Furthermore, as this was a pilot study with a small sample size, it requires replication in a larger sample. Our objective was to inform the study design in terms of recruitment, randomisation, intervention implementation, biomarker collection, blinded assessment procedures and retention for a larger scale hypothesis-testing study. We were able to achieve these aims, whilst also showing that minocycline may be a safe and effective treatment option for those with persistent depressive symptoms. Of note, we found a very strong clinical effect, which was generally supported by secondary outcome measures. In summary, minocycline 200 mg daily added to TAU for 12 weeks was well tolerated and efficacious in improving depressive symptoms in patients with treatment-resistant major depressive episodes. Future studies with larger sample sizes and longer follow-up periods are required to confirm our findings.

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Declaration of conflicting interest

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Chapter 6: Discussion

6.1 Strengths and limitations of systematic review and meta-analysis

Previous meta-analyses of anti-inflammatory treatments in mood disorders have only evaluated the efficacy of these compounds for a specific disorder (e.g. bipolar disorder or MDD), and only for depressive symptoms (Kohler et al., 2014, Rosenblat et al., 2016). As far as I am aware, this is the first meta-analysis that has assessed anti-inflammatory treatments for mania. Furthermore, by combining studies of both bipolar and unipolar depression the current review may have the advantage of investigating inflammation as a trans-diagnostic target for multiple neuropsychiatric disorders; few studies have directly compared inflammation in unipolar and bipolar depression but there do not appear marked differences between these subpopulations (Su et al., 2011, Goldsmith et al., 2016) and increases in statistical power can be achieved by considering the two together.

The benefit of combining studies in BD and MDD is limited by the inability to truly pool the data of all studies. In the current review, studies were pooled based on whether they reported post-treatment depression scores or change in depression scores, but this approach makes it difficult to ascertain what the actual pooled effect size is. A study reporting change versus post-treatment scores should not be a differentiating factor that would mediate effect size, assuming randomization and blinding was effective. Despite this, we were unable to pool standard mean differences (SMDs) from all studies in unipolar and bipolar depression because not all of them used the same symptom rating scales and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) recommends only pooling change in symptom scores with post-symptom severity measures into one mean difference analysis if the same rating scale is used in all studies, which was not the case for trials included in our review. Therefore, the pooled SMDs reported in this meta-analysis may not be indicative of the true effect size of anti-inflammatory agents in the treatment of bipolar and unipolar depression.

Other limitations of the systematic review include the small sample sizes in the majority of studies included, with most showing only small to medium effect sizes with high heterogeneity. It is worth mentioning that a large study of N-acetylcysteine for the treatment of MDD (Berk et al., 2014) had to be excluded from the meta-analysis because full results could not be obtained despite efforts to contact the authors. This study was negative, and had a larger sample size than all six of the studies in the depression meta-analysis combined. It is likely that exclusion of this study has skewed the reported pooled SMD in the meta-analysis of anti-inflammatory treatments for depressive symptoms. The study by Dean et al. (2017) of minocycline as an adjunct for patients with MDD was published after our final search was completed, but if we had included this along with the findings of our pilot RCT in treatment-resistant depression, it is unlikely to have influenced the pooled SMD, given the small sample sizes in both trials and the statistical heterogeneity between studies.

Although there was no evidence of publication bias, this was not assessed statistically due to small numbers and sizes of studies included. Furthermore, treatment durations tended to be short, mostly ranging from 6 to 12 weeks, which means there is no data on long-term adverse effects, tolerability and efficacy of anti-inflammatory treatment. Although efforts were made to summarize adverse effects of the anti-inflammatory interventions, not all studies reported these, limiting a full evaluation of the safety and tolerability of these interventions. It is also important to note that the antidepressant effect of the interventions may be mediated via their effects on physical health comorbidities, although only three studies in which patients recruited were diagnosed with physical health comorbidity were included in the meta-analysis. Finally, the generalizability of 9 studies' findings included in this systematic review is potentially questionable since these trials were all conducted in Iran and trials in high-income countries may yield different results.

6.2 Strengths and limitations of pilot randomised controlled trial

To our knowledge, this is the first RCT of minocycline in patients with treatment-resistant depression (TRD). For the purposes of the trial, treatment resistance was defined as failure to respond to at least two antidepressant medications during the current episode of illness. This definition for TRD was also used by the authors of a large systematic review of 42 randomised trials to reflect the consensus within the literature (Berlim et al., 2007) and in the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders (Bauer et al., 2002). The trial was conducted in Pakistan, in collaboration with investigators from the UK. There is a dearth of high quality trials from low and middle-income countries and such studies from these countries should be encouraged.

The findings of the pilot study show that minocycline may be effective as an adjunct to treatment as usual in patients with treatment-resistant depressive symptoms. Participants randomised to minocycline showed a significant response and the estimated mean reduction in HAMD scores was 18 points. The standardized effect size of 1.21 is large; an effect size of 0.40 or higher has been considered a clinically significant response criterion in previous clinical trials of antidepressant treatments (Faries, 2000). The intervention was also well tolerated in comparison to placebo and there was no significant difference between groups in terms of frequency of adverse events. Most participants in both the minocycline and placebo groups were receiving a SSRI antidepressant as part of their usual treatment. Most participants were also using an augmenting agent (either a second antidepressant or an antipsychotic). The duration since starting their first treatment for depression was over one year for most participants, which suggests that their symptoms were indeed significantly treatment refractory. We did not include a symptom severity threshold requirement for inclusion into the trial as high entry criteria requirements have been associated with greater placebo response rates, and can cause raters to overestimate severity of symptoms at entry but not thereafter, leading to bias (Khan et al., 2007).

The results of our pilot add to the growing evidence that minocycline may have antidepressant properties. Open-label studies of minocycline augmentation for unipolar depression have supported this claim (Miyaoka et al., 2012). A more recent RCT of minocycline monotherapy in patients with a HIV diagnosis and mild to moderate depression (HAMD < 18) found significantly greater improvements in HAMD scores in patients in the minocycline group compared to those in the placebo group. There were also more partial responders in the minocycline group compared to the placebo group (Emadi-Kouchak et al., 2016). Another open-label study of minocycline added to treatment as usual (TAU) in 29 patients experiencing a DSM-IV-TR major depressive episode with a diagnosis of bipolar I or II disorder, found that adjunctive minocycline was associated with a reduction in depressive symptom severity from baseline to week 8 on the Montgomery-Asberg Depression Rating Scale (MADRS) scores ($P<0.001$, $d=0.835$), HAMD-17 ($P<0.001$, $d=0.949$) and CGI-S ($P<0.001$, $d=1.09$). Improvement in psychomotor speed, but not verbal memory or executive function, was observed only amongst individuals exhibiting a reduction in depression severity ($P=0.007$, $d=0.826$). Analysis of biomarkers in this study showed that levels of IL-12/23p40 ($P=0.002$) were increased, while levels of IL-12p70 ($P=0.001$) and C-C motif chemokine ligand 26 (CCL26) ($P<0.001$) were reduced from baseline to week 8. A reduction in CCL26 levels was associated with a less favourable treatment response ($P<0.001$) (Soczynska et al., 2017).

A study by Dean et al. (2017) also published after the included systematic review was in press, provides more evidence that minocycline may play a role in the treatment of depressive illness. In this 12-week RCT, a total of 71 adults with unipolar DSM-IV major depressive disorder were randomised to minocycline 200mg daily added to TAU or placebo added to TAU. The participants recruited to this study did not need to meet criteria for treatment resistance. Although the results revealed no significant difference in the primary outcome (MADRS scores) between groups, there were significant differences on secondary outcome measures. At week 12, the minocycline group showed significant improvements on Clinical Global Impression-Improvement score -

effect size (ES) (95% confidence interval) = -0.62 [-1.8, -0.3], p = 0.02; Quality of Life Enjoyment and Satisfaction Questionnaire score - ES = -0.12 [0.0, 0.2], p < 0.001; and Social and Occupational Functioning Scale and the Range of Impaired Functioning Tool score – ES = 0.79 [-4.5, -1.4], p < 0.001. These effects remained at the follow-up (week 16), and Patient Global Impression also became significant, ES = 0.57 [-1.7, -0.4], p = 0.017 (Dean et al., 2017).

The findings of the study by Dean and colleagues may differ from ours because of the clinical characteristics of the participants included. Our study included only participants that had failed to respond to at least two antidepressants within the same episode and as such, the results may indicate that minocycline may be more effective for those patients that have a degree of treatment resistance. It has been hypothesized that a sub-group of patients with TRD have an underlying activated inflammatory response, with studies showing that TRD patients have activation of monocytes and microglia, which leads to increased production of pro-inflammatory cytokines (e.g. IL-6 and TNF-α) and acute-phase proteins (i.e. CRP) (Grosse et al., 2016, Strawbridge et al., 2015). Given its broad anti-inflammatory actions on these pathways, minocycline may inhibit the inflammatory response more effectively in TRD patients leading to greater improvements in mood compared to those patients that are not treatment resistant.

However, the results of the pilot trial should be considered under the light of certain limitations. One of the main concerns about the findings was the discrepancy between the primary outcome measure i.e. HAMD scores and the secondary outcome, the patient-rated PHQ-9. There was large statistically significant response on the clinician-rated HAMD and CGI measures in the minocycline group but a smaller response on the PHQ-9, which was not statistically significant. In the placebo group, there was no response on the HAMD and CGI measures but a large response on the PHQ-9. The absence of a response as measured by HAMD scores in the placebo group may reflect the chronicity and initial severity of the sample. A total of 95% of the participants receiving either treatment had been receiving treatment for MDD for at least 12 months.

Studies have indicated that the natural history of illness and specifically, longer duration of current illness can reduce the placebo response (Rutherford & Roose, 2013). Secondly it has been found that placebo response decreases with increasing severity of baseline depression scores, with a recent study finding that placebo response significantly declined as baseline HAMD increased (particularly as it exceeded a score of 25) (Fournier et al., 2010). The mean baseline HAMD score in the placebo group in the current study was 32.6 with only 3 participants scoring less than 25.

Lack of correlation between clinician and patient-rated outcomes are not uncommon and previous larger trials of antidepressant treatments have also reported similar discrepancies (Targum et al., 2013). The reasons for the discrepancy in this pilot trial are unclear although participant motivation to be involved in the trial, a heightened awareness of symptoms at baseline, and the experimental environment itself (i.e. expectancy biases) may have affected the patient's perception of depressive symptoms and influenced self-rating during the study. It is also prudent to consider the robustness of blinding during the study; although every attempt was made to maintain a strong blind, this was not formally measured. The degree of discrepancy between outcome measures in the context of a small sample size could raise questions about the success of blinding and potential measurement bias. Inter rater reliability was not formally measured and recorded although Masters level clinical psychologists, who were trained by local principal investigators, carried out all assessments.

Another potential limitation of the study is that all participants recruited to the study were permitted to change their regular medications under the supervision of their treating team. Although it can be argued that changes to TAU would add “noise” to the treatment signal, we were able to record all medication changes for each participant and found that these changes were similar between the groups. However, the fact that we did not measure medication adherence is a shortcoming of the study. Future trials should check participant treatment adherence through pill counts and/or assessment

scales such as the Morisky measurement of medication adherence (MMAS-4) (Morisky, 1986).

This study was designed as an exploratory, pilot RCT and for studies of this nature the sample size is appropriate (Julious, 2005; US FDA 2016). Nonetheless the small sample size means that any estimates of effect are unlikely to be robust. The small sample size also limits the evaluation of how representative the sample is and also the comparability of the two treatment arms. The generalizability of our results is limited by the fact that this was a single centre study conducted in Karachi, Pakistan. Larger, multi-centre studies in other settings are required to determine whether our findings are applicable to other populations, particularly those in high-income countries. Lastly, this was only a 12-week study and since participants were followed up for a relatively short period of time, we are unable to comment on the long-term efficacy and safety of minocycline as an augmenting agent in treatment-resistant depression.

6.3 Issues related to conducting clinical trials in a low and middle-income country

In this section I will discuss factors that may make conducting a clinical trial in a low and middle-income country (LAMIC) such as Pakistan, different from conducting trials in higher-income countries. Since there is a paucity of data on Pakistan-specific demographics or national epidemiologic studies conducted with any standardized diagnostic interviews, this discussion is narrative and based on my experience during the pilot study.

It is important to recognize the benefits of conducting clinical trials in LAMIC. As mentioned previously there is a dearth of literature from these regions and more studies should be encouraged for several reasons. Firstly, it has been reported that it may be easier to detect a signal in clinical trials and to separate the signal from 'noise' in the analysis of data from a LAMIC. This is thought to occur due to cultural and religious factors, that lead to patients with severe mental illness in countries like Pakistan being less likely to have comorbid psychiatric conditions such as alcohol and substance

misuse, which would make the sample diagnostically cleaner (Andrade, 2013). Furthermore, research participants in Pakistan usually have strong family support, and family members tend to ensure medication adherence and often bring participants to follow-up appointments. This helps maintain adherence to the study protocol and maintains high study retention rates, as in the case of our pilot trial, in which the attrition rate was only 17%.

Other advantages of conducting trials in LAMIC include the practical benefits for the investigators. These countries are densely populated; recent census results from Karachi, the city where our study was conducted, revealed a population of 14.9 million although these results have been widely disputed and the actual figure is more likely to be over 20 million (Rana, 2017). Such large populations put huge pressure on local healthcare systems to cater to the needs of people with mental illness and so recruitment targets in clinical trials are met with greater speed. In addition, salaries, cost of living and clinical trial expenses are much lower, so trials can be conducted with more modest funding. As patients are used to a paternalistic model of healthcare, dropout rates are often lower than in other regions. Another important advantage to researchers is that in countries such as Pakistan almost all investigators and research personnel are fluent in English, which is the language in which study protocols are drafted.

Clinical trials conducted in LAMIC are also important as they contribute to significant capacity building. The local study team is trained in Good Clinical Practice and research processes, which empowers local academic centers to design and conduct their own studies. Patients that participate in trials also gain because they receive high quality, individualized care and follow-up at no cost and often have their travel expenses for assessment visits reimbursed. Finally, the broader society within LAMIC also benefits from such trials because locally relevant pharmacodyanmic and pharmacokinetic data is produced that informs local clinicians and policy makers.

However, there are also important challenges to address when conducting trials in LAMIC. The aforementioned pressure on local health services and in particular, the scarcity of mental health services in countries like Pakistan, may contribute to larger effect sizes in clinical trials, which means that these have to be interpreted with some caution as findings may not be replicable in high-income countries. Other challenges include the translation of consent forms and rating scales, which is sometimes done with only superficial validity and without confirming the psychometric properties of the translated scales. Given the poor literacy rates in countries such as Pakistan, research participants who have lower literacy and education levels are at risk of exploitation. We overcame this issue by ensuring that the research team explained the study to all participants in the presence of a witness (usually a care giver) and allowed them up to 24 hours to take the study information sheet home and discuss their participation with relatives and friends before providing consent. Literate participants signed the consent forms but, if the participant could not write their name, they placed a thumbprint on the consent form, which was countersigned by the witness. This approach is not standard practice in all settings and is not deemed mandatory by regulatory bodies. Another important challenge that we and other researchers have faced when conducting trials in countries such as Pakistan is the considerable cultural and psychological significance that participants place on drawing of blood samples, especially if this involves storage of samples for later analysis. Several participants in our pilot study refused to consent to drawing of blood samples, which made it impossible to draw inference of any mechanistic hypothesis on the mode of action of minocycline from the limited biomarker data that was analyzed. Such challenges must be taken in to account when designing clinical trials in LAMIC and perhaps it would be more appropriate that the provision of blood samples be stipulated as a requirement for recruitment if the study has a mechanistic component that requires the evaluation of biomarkers.

6.4 Potential mechanisms of minocycline's putative antidepressant action

Since it has been postulated that the potential antidepressant mechanisms of action of minocycline is through an anti-inflammatory effect, we attempted to measure

Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) levels at baseline and at the end of treatment. Both biomarkers have been shown to be reliable indicators of systemic inflammation (Cameron & Kelvin, 2000). Unfortunately, in the included pilot study many participants refused to consent to the provision of blood samples. This may be due to cultural factors and the religious significance of drawing blood, particularly during religious periods such as the month of Ramadan. I have conducted analysis of the biomarker data that was available but given the small sample size and amount of missing data, drawing any inference from these results would be unwise. The missing data is due in part to the limited funding for the study, which did not allow for assertive follow-up of participants to ensure bloods were drawn at both baseline and end-point. I will try and address this in the planned replication study, which I hope will have more substantial funding. Future studies of minocycline should also include measurement of inflammatory cytokines such as IL-6 and TNF-α, amongst others, to determine the association between changes in inflammatory biomarkers and improvement in depressive symptoms.

As summarized earlier, inflammation has been shown to cause serotonin dysfunction, disturbances in the HPA axis, microglial activation and the release of neurotoxic metabolites leading to neuroplastic changes. All of these factors may be involved in the manifestation of a depressive syndrome. I hypothesize that minocycline acts on several of these mechanisms to produce an antidepressant effect. I have previously summarized evidence that shows how microglia plays a significant role in the neuroinflammatory processes that are implicated in the aetiology of depression. Minocycline has shown to be an inhibitor of microglial activation (Soczynska et al., 2012) and has also shown to decrease depressive and anxiety-like behaviours in mice whilst reducing pro-inflammatory cytokines (i.e. TNF and IL-1B) and glucocorticoids (Majidi et al., 2016). The kynurenine pathway, another inflammatory pathway purported to play a part in the pathophysiology of depression, is also modulated by minocycline. Pro-inflammatory cytokines can activate the enzyme indoleamine 2,3-dioxygenase (IDO). Increased IDO activity decreases synthesis of serotonin from tryptophan, leading to the production of

pro-depressant and neurotoxic metabolites (Grosse et al., 2016). In animal studies, minocycline has been shown to block the pro-inflammatory cytokine TNF-α, which activates IDO (O' Connor et al., 2009, Liu et al., 2015).

Another important consideration when examining minocycline's putative antidepressant action is its pharmacokinetic properties and possible interactions with antidepressant drugs. There is limited data on the metabolism of minocycline (Nelis & de Leenheer, 1982) but it is plausible that it is mediated by Cytochrome P450 enzymes, which are involved in the metabolism of many commonly used antidepressants. Further, recent in vitro studies indicate that minocycline may exert local inhibition of cytochrome p450 enzyme activity in neuronal cells (Regen et al., 2016). If minocycline does inhibit one or more cytochrome p450 enzymes either by competition for metabolism or a direct mechanistic effect, it may also be contributing to enhanced antidepressant activity by increasing the plasma or local concentration of antidepressant drugs.

In addition to its anti-inflammatory and pharmacokinetic properties, minocycline has been shown to be neuroprotective and may directly promote neurogenesis (Soczynska et al., 2012). These neuroprotective and neurotrophic properties may also be involved in its potential antidepressant actions. Studies have shown that minocycline increases the number of integrated newborn hippocampal neurons by promoting the survival of newly divided cells (Liu et al., 2007), and that it also increases the survival of neurons in animal models of ischemia (Yrjanheikki et al., 1998). Other animal studies have reported that minocycline reduces tissue damage and cavitation after spinal cord injury (Festoff et al., 2006), and restores impaired hippocampal neurogenesis after lipopolysaccharide (LPS)-induced inflammation (Ekhdal et al., 2003).

Although the exact mechanisms by which it affects neurogenesis and neuroprotection remain unknown, it has been shown to modulate systems (e.g. inflammation) that affect neuroplasticity. Neuroplasticity is the concept that the brain can change in structure

and function in response to environmental demands. Mood disorders are marked by abnormalities in brain structure and function, as well as impairments in cognition (Kempton et al., 2011; Konarski et al., 2008). Abnormalities in neuronal apoptosis have been hypothesized to contribute to the brain structural changes that occur in mood disorders (Szuster-Ciesielska et al., 2008). Minocycline has been shown to have anti-apoptotic and anti-oxidative properties within the central nervous system (Soczynska et al., 2012). Studies show that minocycline is anti-apoptotic through three main mechanisms: 1) by reducing the release of apoptotic agents from mitochondria 2) enhancing the release of anti-apoptotic factors 3) by reducing oxidative stress (Noble et. al, 2009). Minocycline exerts antioxidant properties by suppressing free radical generation and by directly scavenging free radicals (Kraus et al., 2005). This reduces oxidative stress, which been hypothesized to play a role in the pathophysiology of bipolar disorder and depression. In both disorders, increased levels of free radicals have been reported (Andreazza et al., 2008; Dhir & Kulkarni, 2011; Suzuki et al., 2001).

Another important mediator of neuroplasticity in mood disorders is the excitatory neurotransmitter glutamate. Abnormal levels of glutamate have been found in the plasma, cerebrospinal fluid and brain tissue of patients suffering from mood disorders (Sanacora et al., 2012). In depressed patients decreased levels of glutamate metabolites have been observed, whereas in bipolar patients these are increased (Yuksel & Ongur, 2010). In bipolar patients, glutamate levels may be dependent on the mood episode with studies showing that the glutamine/glutamate ratio is reduced in the depressive phase of illness but increased during manic episodes (Sanacora et al., 2012). These glutamatergic abnormalities may be associated with neuroinflammatory processes in a sub-group of mood disorder patients. It has been proposed that disturbances to the kynurenine pathway may lead to glutamatergic disturbances in some patients with mood disorders rather than due to a direct impact on glutamate transporters or receptors (Steiner et al., 2012). The increased QUIN/KYNA ratio may lead to excitoxicity causing astrocyte loss. Astrocytes are the main cells responsible for glutamate reuptake from the extracellular space and in their absence glutamate can cause prolonged

synaptic activation leading to neurotoxicity, production of free radicals and apoptosis (Choudary et al., 2005; Muller & Schwarz, 2007; Myint 2012). Minocycline has been shown to indirectly modulate glutamate transmission in several animal studies (Baptiste et al., 2004; Nie et al., 2010, Song et al., 2006). This effect may be due to minocycline's anti-inflammatory and anti-oxidative properties, which result in reduced production of QUIN in the kynuerenine pathway (cf. Figure 4) (Myint 2012).

The evidence summarized above would indicate that inflammation is associated with multiple interacting pathways including apoptotic, neurotrophic, oxidative, and glutamatergic pathways, which may be involved in the pathophysiology of mood disorders. However, a wider search in this area shows that the evidence remains conflicting and that it is most likely that the pathophysiology of mood disorders is highly heterogeneous, which makes treatment trials for these conditions especially challenging. Current evidence shows that minocycline may exert effects on several of the interacting systems that may be implicated in the pathophysiology of mood disorders. The pilot trial of minocycline as an add-on treatment for patients with treatment-resistant depression provides vital proof-of-concept evidence that it may have therapeutic potential in these common and often disabling conditions. I hope that our findings will inform the development of more rigorous, larger scale efficacy studies that will include robust mechanistic components such as measurement of inflammatory biomarkers and/or neuroimaging. The results of these studies will determine whether minocycline is a viable treatment option in an identifiable sub-group of patients with mood disorders.

Chapter 7: Conclusion

7.1 Implications for future research

The findings from the research conducted during my MD (Res.) show that current evidence for the use of anti-inflammatories as treatments for mood disorders remains inconsistent. Current studies are limited by small sample sizes, short durations, differing baseline symptomatology and poorly defined illness durations, which makes it impossible to provide recommendations on the routine clinical use of these agents in the treatment of bipolar disorder and MDD. The most investigated anti-inflammatory treatment thus far is celecoxib, with many studies reporting antidepressant effects when used as an adjunct or as monotherapy (Müller et al., 2006, Akhondzadeh et al., 2009, Abbasi et al., 2012, Jafari et al., 2015, Majid et al., 2015). There are also indications that celecoxib may have antimanic properties, although this assumption is based on a small study not evaluating long-term effects on response and remission (Arabzadeh et al., 2015). Although it has been reported that non-steroidal anti-inflammatory drugs carry an increased risk for gastrointestinal (Wolfe et al., 1999) and cardiovascular (Mukherjee et al., 2001) adverse effects, this has not been supported by my analysis. However, it is important to note that some studies did not provide any comment on adverse effects (Berk et al., 2012, Kargar et al., 2015, Magalhães et al., 2013). Furthermore, given the short study period for many of the trials conducted thus far, it is possible that adverse effects were not identified in the study timeframe. Given these important caveats, it is imperative to proceed cautiously before implementing celecoxib or other anti-inflammatory treatments in routine clinical practice, and the potential therapeutic benefits in mood disorder must be balanced against the risk of adverse effects.

Given the small number of studies that have investigated cytokine inhibitors, N-acetylcysteine and minocycline for the treatment of mood disorders, further high quality controlled clinical trials are needed to contribute to the current body of evidence. Although the results of our pilot study indicate that minocycline has a

potential role as an augmentation strategy in patients with treatment-resistant depression, this was only a pilot trial with a small sample size and more studies are required. The objective of our pilot study was to inform the study design in terms of recruitment, randomization, intervention implementation, biomarker collection, blinded assessment procedures and retention, for a larger scale hypothesis testing study. We achieved these aims, whilst also showing that minocycline may be a safe and effective treatment option for those with persistent depressive symptoms. Of note we found a very strong clinical effect, which was generally supported by secondary outcome measures. Future studies with larger sample sizes and longer follow-up periods, incorporating robust mechanistic components are required to confirm our findings and to determine the mode of potential antidepressant action of minocycline. Similarly, more large-scale clinical trials of celecoxib and other anti-inflammatories for patients with depression (both unipolar and bipolar) and mania are warranted. Such trials will assess longer-term safety and tolerability as well as effects on response and remission rates in both major depressive disorder and bipolar disorder.

I suggest that future treatment trials should also include the measurement of biomarkers to identify whether the clinical benefits of anti-inflammatory medications occur alongside a change in inflammatory activity, or in only a biological sub-group of patients experiencing a mood disorder. Studies have already found that patients with both depression and bipolar disorder may have abnormal levels of circulating inflammatory markers (Goldstein et al., 2009, Howren et al., 2009, Dowlati et al., 2010). A recent meta-analysis has found that in MDD, these levels may normalize with treatment and the authors identified TNF-α as a potential marker for treatment-resistant depression (Strawbridge et al., 2015). However, plasma cytokines are strongly affected by environmental factors (e.g. age, gender, exercise, obesity, insulin resistance, smoking), and by the heterogeneity of mood disorder itself, and so exhibit high inter-individual variance. Instead it has been suggested that measuring the pro-inflammatory state of monocytes, the main cytokine producers, via gene expression may be a more sensitive way to detect inflammation (Carvalho et al., 2014, Grosse et al., 2015). Future

RCTs of anti-inflammatory medications should attempt to incorporate these putative biomarkers to determine whether the mechanism of any antidepressant or antimanic action is due to the inhibition of inflammatory processes. The results of such studies may provide clinicians with clear guidelines on when to implement anti-inflammatory treatment for patients experiencing mood disorders that do not respond to conventional treatments.

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Appendix

Systematic review quality assessment tool

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

Study Name:

COMPONENT RATINGS

. **A) SELECTION BIAS**

. **(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?**

. 1 Very likely

. 2 Somewhat likely

. 3 Not likely

. 4 Can't tell

. **(Q2) What percentage of selected individuals agreed to participate?**

. 1 80 - 100% agreement

. 2 60 – 79% agreement

. 3 less than 60% agreement

. 4 Not applicable

. 5 Can't tell

. **RATE THIS SECTION STRONG MODERATE WEAK**
See dictionary 1 2 3

. **B) STUDY DESIGN**

. **Indicate the study design**

. 1 Randomized controlled trial

. 2 Controlled clinical trial

. 3 Cohort analytic (two group pre + post)

. 4 Case-control

. 5 Cohort (one group pre + post (before and after))

. 6 Interrupted time series

. 7 Other specify _____

. 8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION STRONG MODERATE WEAK
See dictionary 1 2 3

C) CONFOUNDERS

. **(Q1) Were there important differences between groups prior to the intervention?**

. 1 Yes

. 2 No

. 3 Can't tell

. **The following are examples of confounders:**

. 1 Race

. 2 Sex

. 3 Marital status/family

. 4 Age

. 5 SES (income or class)

. 6 Education

. 7 Health status

. 8 Pre-intervention score on outcome measure

. **(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?**

. 1 80 – 100% (most)

. 2 60 – 79% (some)

. 3 Less than 60% (few or none)

. 4 Can't Tell

. **RATE THIS SECTION STRONG MODERATE WEAK**
See dictionary 1 2 3

D) BLINDING

. **(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?**

. 1 Yes

. 2 No

. 3 Can't tell

. **(Q2) Were the study participants aware of the research question?**

. 1 Yes

. 2 No

. 3 Can't tell

. RATE THIS SECTION STRONG MODERATE WEAK
See dictionary 1 2 3

E) DATA COLLECTION METHODS

. **(Q1) Were data collection tools shown to be valid?**

. 1 Yes

. 2 No

. 3 Can't tell

. **(Q2) Were data collection tools shown to be reliable?**

. 1 Yes

. 2 No

. 3 Can't tell

. RATE THIS SECTION STRONG MODERATE WEAK
See dictionary 1 2 3

F) WITHDRAWALS AND DROP-OUTS

. **(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?**

. 1 Yes

. 2 No

. 3 Can't tell

. 4 Not Applicable (i.e. one time surveys or interviews)

. **(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).**

. 1 80 -100%

. 2 60-79%

. 3 less than 60%

. 4 Can't tell

. 5 Not Applicable (i.e. Retrospective case-control)

. RATE THIS SECTION STRONG MODERATE WEAK
See dictionary 1 2 3

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

. 1 80 -100%

. 2 60-79%

. 3 less than 60%

. 4 Can't tell

(Q2) Was the consistency of the intervention measured?

. 1 Yes

. 2 No

. 3 Cant tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results

4. Yes

5. No

6. Cant tell

H) ANALYSES

. **(Q1) Indicate the unit of allocation (circle one)**

. community organization/institution practice/office individual

. **(Q2) Indicate the unit of analysis (circle one)**

. community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

. 1 Yes

. 2 No

. 3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

. 1 Yes

. 2 No

. 3 Can't tell

GLOBAL RATING COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A SELECTION BIAS STRONG MODERATE WEAK
123
B STUDY DESIGN STRONG MODERATE WEAK
123
C CONFOUNDERS STRONG MODERATE

WEAK
123
D BLINDING STRONG MODERATE WEAK
123
E DATA COLLECTION METHOD
STRONG MODERATE WEAK
123
F WITHDRAWALS AND DROPOUTS
STRONG MODERATE WEAK
1 2 3 Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1 STRONG (no WEAK ratings)

2 MODERATE (one WEAK rating)

3 WEAK (two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?
No Yes

If yes, indicate the reason for the discrepancy

. 1 Oversight

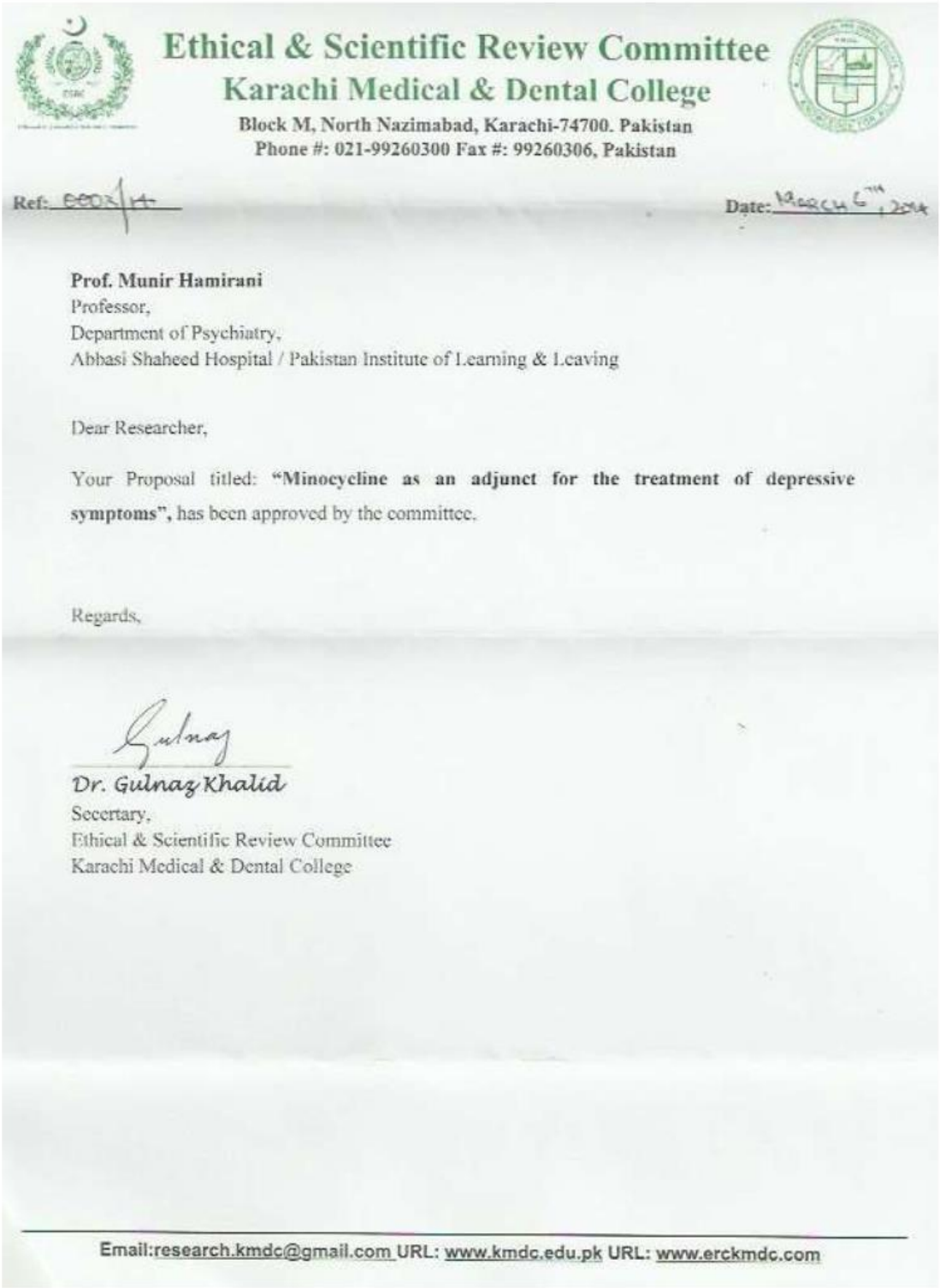
. 2 Differences in interpretation of criteria

. 3 Differences in interpretation of study

Final decision of both reviewers (circle one):

1 STRONG

Ethics approval letter



Ethical & Scientific Review Committee
Karachi Medical & Dental College
Block M, North Nazimabad, Karachi-74700. Pakistan
Phone #: 021-99260300 Fax #: 99260306, Pakistan

Ref: EERC/14 Date: MARCH 6TH, 2014

Prof. Munir Hamirani
Professor,
Department of Psychiatry,
Abbasi Shaheed Hospital / Pakistan Institute of Learning & Leaving

Dear Researcher,

Your Proposal titled: **"Minocycline as an adjunct for the treatment of depressive symptoms",** has been approved by the committee.

Regards,

Gulnaz

Dr. Gulnaz Khalid
Secretary,
Ethical & Scientific Review Committee
Karachi Medical & Dental College

Email:research.kmdc@gmail.com URL: www.kmdc.edu.pk URL: www.erckmdc.com

Consent form

Minocycline as an adjunct treatment for treatment resistant depressive symptoms.

Consent Form

Please initial each Box

1	I confirm that I have read and understand the information leaflet dated Version 1 for the above study and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that any quotes made by me may be used in publications, and that all quotes will be anonymised before use	☐
4	I agree that my given information will be by stored under the supervision of research team anonymously and will be used for publications.	☐
5	I agree to take part in the above study	☐

Name of Participant	Signature	Date
Researcher	Signature	Date

1 copy for participant; 1 copy for researcher

Consent form (in Urdu)

Minocycline as an adjucnt treatment for treatment resistant depressive symptoms

اجازت نامہ

Pt.'s Identification No. _____

1۔ میں تصدیق کرتا/کرتی ہوں کہ میں نے معلوماتی صفحہ جو کہ اس تحقیق کے متعلق ہے پڑھ اور سمجھ لیا ہے اور مجھے اس بارے میں سوال کرنے کا پورا حق ہے ☐

2۔ میں نے اس بات کو پوری طرح سمجھ لیا ہے کہ اس تحقیق میں میری شمولیت رضا کارانہ ہے اور مجھے یہ حق حاصل ہے کہ میں جب چاہوں بغیر وجہ بیان کئے اس تحقیق سے علیحدہ ہو سکتا/ہو سکتی ہوں۔ میرے اس عمل سے میرے علاج پر کوئی فرق نہیں پڑے گا۔ ☐

3۔ میں اس بات پر رضامند ہوں کہ تحقیق داں اور دوسرے ٹیم کے افراد میرے علاج سے متعلق تمام معلومات کو پڑھ اور دیکھ سکیں۔ ☐

4۔ مجھ سے متعلق تمام معلومات جس میں میرا نام، پتہ وغیرہ شامل ہوں، اُن معلومات کو میری شناخت ظاہر کئے بغیر استعمال کیا جائے گا اس کا مطلب یہ ہے کہ میری شناخت کو اس تحقیق کے دوران اور تحقیق کے بعد بھی صیغہ راز میں رکھا جائے گا۔ ☐

5۔ میں تصدیق کرتا/کرتی ہوں کہ مجھے اس تحقیق کا مقصد اور نوعیت واضح طور پر سمجھا دی گئی ہے اور اس کے دوران ہونے والے ممکنہ خطرات سے بھی آگاہ کر دیا گیا ہے۔ ☐

6۔ میں اس تحقیق میں حصہ لینے کے لئے رضامند ہوں۔ ☐

اس تحقیق میں حصہ لینے والے کو تین ماہ تک دوائیں مفت فراہم کی جائینگی۔

نام: ..... تاریخ: ..... دستخط: .....

اجازت لینے والے کا نام: ..... تاریخ: ..... دستخط: .....
(اگر تحقیق کرنے والے سے مختلف ہے)

تحقیق کرنے والے کا نام: ..... تاریخ: ..... دستخط: .....

Patient Information Sheet

Minocycline as an adjunct treatment for treatment-resistant depressive symptoms: pilot randomised controlled trial

Patient Information Leaflet

Purpose of the Research Study:

You are being invited to participate in a research study designed to check the benefits of minocycline as an augmentation treatment for treatment-resistant depression. The purpose of this study is to evaluate whether minocycline added to treatment as usual (TAU) is effective in the treatment of treatment-resistant depression. We aim to check whether the addition of minocycline to TAU for 12 weeks leads to an improvement in depressive symptoms as compared to the placebo. In addition, we also plan to investigate any associated impact minocycline has on inflammatory biomarkers and if this is linked to an improvement in mood.

Procedure:

You will be approached by our research staff or your treating consultant, who will introduce the study to you. After checking that you meet the inclusion criteria, a written patient information sheet containing all study details in Urdu and at least 48 hours will be given to you to decide if you would like to participate in the study. Once you have read and understood the study and if you are willing to participate, an appointment will be arranged to obtain written consent. During this appointment the research team will complete all other assessments, which are commonly in research studies and are used across the world. You will be asked to provide two blood samples for the analysis of the relationship between minocycline and inflammatory markers. You will be randomized either to receive minocycline added to treatment as usual (TAU), or a placebo tablet added to TAU. After completing initial assessments, you will be provided with study medication to take along with your routine medicine for three months.

You will be requested to attend follow-up sessions regularly and advised not to take any illicit substances. Women of childbearing age will be required to use effective contraception throughout the study period.

Your Treatment:

You will be randomly assigned into one of these two treatment groups, either receiving minocycline added to Treatment as Usual (TAU), or placebo added TAU for the duration of twelve weeks.

- Minocycline 100mg daily, increased to 200 mg daily after 2 weeks
- Placebo tablets

Follow-up Sessions:

The timings of the sessions will be scheduled according to your convenience. Follow-up assessments will be at weeks 2, 4, 8 and 12. The purpose of these follow-ups is to collect information regarding your health and wellbeing.

What are the side effects of participation?

Minocycline is a well-tolerated drug but like any other medicine, it has its side effects. For example, you may feel dizziness, weakness, muscle pain, fever or weight gain during the course of study. Your health will be monitored at each follow-up and in case of any serious adverse effects, we will respond to any concerns immediately and stop the study medication. The study physician will conduct a complete physical health check and the treating consultant will provide any treatment required accordingly. You may also feel slight discomfort during collection of blood samples. Respecting your rights, you will be free to withdraw from the study at any point, which will not affect your usual treatment.

What will be possible benefits participating?

Our prediction is that minocycline may be effective in reducing depressive symptoms and so there may be a chance that you feel an improvement in your mood by participating in the study. Furthermore, you will have regular follow-up with our research team to provide frequent monitoring of your physical and mental health. Finally, the findings of this study will contribute to future evidence-based treatment recommendations and research in mental health.

Financial Consideration:

Transport expenses will be reimbursed to you at each follow-up.

There are no additional costs to you.
Study medication will be given free of cost to all participants.

Aavailable treatment alternatives:

Participants in both study arms will continue with their treatment as usual.

Available medical treatments for adverse experiences:

To keep a close check on your health status your symptoms will be monitored on a weekly basis. You will receive a physical examination by the study physician who will review your medical history once you are enrolled in the study. The research team will contact you every two weeks until study completion. The clinical team and consultant psychiatrist will continue to oversee your routine care.

All study-related safety concerns will be the responsibility of the local principal investigators, who can be contacted at any time through the research team. You will be given 24-hour emergency contact numbers, which will be operated by trained staff nurses. These nurses have access to medical consultants for advice and consultation.

Will my participation be confidential?

All the information collected during this trial will be kept strictly confidential. Data collection, protection and wastage will be completed according to the 1998 Data Protection Act of UK. You will be assigned a unique ID number during the study and all your data will remain anonymous by using code numbers on files. Your identifying information taken on demographic questionnaires will be kept in locked cabinets and only the trial manager will have access to it when needed. Results of the study including laboratory or any other data may be published for scientific purposes or inspected by the sponsor but any identifying information will be excluded.

If I discontinue the research then what will happen?

You have the right to withdraw from the study at any time; it will not affect your treatment at all. There will be no penalty and loss of benefits to which you are otherwise entitled, i.e. regular assessments, follow up and blood tests. Alternatively, you can withdraw from the treatment and continue to engage in assessment, if you agree to this. You will be provided with any new information discovered during the course of this study that may relate to, or influence your willingness to continue participating.

Available Source of Information:

If you have questions about this study, feel free to contact:

Trial Manager:
Mr. Ameer Bukhsh Khoso
021-35871845

In case of a research-related emergency, call:

Day Emergency No & Address:

Pakistan Institute of Learning and Living Zamzama office.
Phone: 02135871845

Night Emergency No & Address:

REMEDIAL CENTRE HOSPITAL
ADDRESS: D-9, BLOCK-I, NORTH NAZIMABAD, KARACHI
24 Hours Hotline No: 021-36673040

AUTHORIZATION:

I have read and understood this consent form, and I volunteer to participate in this research study. I voluntarily choose to participate but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I will receive a copy of this form and I acknowledge that nothing in this consent form is intended to replace any applicable Federal, state, or local laws.

Participant Name: _____

Date: _____

Participant Signature: _____

Signature of Person obtaining consent: _____

Date: _____

Patient Information Sheet (in Urdu)

حصہ لینے والوں کے لئے معلوماتی کتابچہ

ڈپریشن میں منفی علامات پر مینوسائکلین کے فوائد:

ہم آپ کو ایک تحقیق میں حصہ لینے کی دعوت دیتے ہیں۔ اس لیے کتابچے میں اس بات کی وضاحت کی گئی ہے کے یہ تحقیق کیوں کی جارہی ہے اور اس میں کیا شامل ہے۔ شمولیت کے لئے کوئی جلدی نہیں ہے، اور سوالات کے لئے کافی وقت ہے۔ اگر آپ چاہیں تو دوسروں سے بھی اس کے متعلق بات کریں۔ اگر آپ شمولیت کے لئے رضامند ہیں تب بھی آپ کسی کی ناراضگی کے بغیر کسی بھی وقت اپنی پسند کے مطابق تحقیق سے علیحدہ ہو سکتے ہیں۔

یہ تحقیق کیوں کی جارہی ہے؟

حالیہ تحقیق سے معلوم ہوا کے مشہور اینٹی بائیوٹک مینوسائیکلین کھانے سے ڈپریشن اور شیزوفرینیا کے علاج میں بہتری پیدا ہوتی ہے۔ اس تحقیق کا مقصد یہ ہے کے مینوسائکلین کی فائدے دیکھے جائیں اور دیکھا جائے کے یہ دوا کیسے کام کرتی ہے۔ علاج کے نئے طریقے ڈپریشن کو کم کرنے میں بہت موثر ہیں۔ ڈپریشن کے مریضوں میں احساسات، زندگی اور دوسروں کے ساتھ میل جول سے خوشی حاصل کرنے میں کمی آجاتی ہے۔ اگر ڈپریشن کی بیماری واپس نہ آئے تو ان چیزوں میں بہتری پیدا ہو سکتی ہے لیکن یہ زیادہ عرصے تک رہنے والے مسائل بھی بن سکتے ہیں۔ سوچنے کی صلاحیت اور یادداشت پر بھی اثر ہوتا ہے۔ تحقیقات بتاتی ہیں کے مینوسائیکلین ڈپریشن کی علامات کے علاج کے لیئے فائدہ مند ہے۔

مینوسائیکلین ایک عام اینٹی بائیوٹک ہے جو کئی سالوں سے مہاسوں کی بیماری کے علاج کے طور پر استعمال کی جارہی ہے۔ تاہم اس کے اور بھی عمل ہیں جو دماغ کی مختلف بیماریوں کے علاج کے لئے فائدہ مند ہو سکتے ہیں۔

مینوسائیکلین درج ذیل طریقوں سے کام کر سکتی ہے:

1۔ دماغ میں موجود کیمیائی مادے ،،گلوٹامیٹ،، پر اثر کے ذریعے دماغی کے کام میں تیزی لاتی ہے۔ ہم اسے دماغ کے معائنے اور کمپیوٹر پر کیئے جانیوالے کاموں کے ذریعے ٹیسٹ کریں گے

2 ۔دماغ کے خلیوں کے درمیان رابطے کو قائم کرنا۔ اس سے سوچنے کی صلاحیت اور متحرک رہنے کی طاقت میں بہتری ہو سکتی ہے۔ دماغ کا معائنہ ہمیں بتائے گا کے ایسا ہوا یا نہیں۔

جب ہم مینو سائیکلین کا عمل سمجھ لیں گے، تو بہتر دوائیں پیدا کی جا سکتی ہیں جو متعلقہ کام پر فوکس ہوں۔

اس تحقیق میں روٹین کے علاج کے ساتھ تین مہینے تک مینو سائکلین لینا ہو گی۔ اس علاج کے شروع ہونے سے پہلے اور آخری (تیسرے) مہینے پر آپ کے دماغ کا معائنہ ہو گا۔

مجھے کیوں دعوت دی گئی:

ہم آپ کو شرکت کی دعوت اس لئے دے رہے ہیں کے آپ ڈپریشن کا علاج کروا رہے ہیں۔ آپکے ڈاکٹرز کی یہ رائے ہے کے ہو سکتا ہے آپ اس تحقیق میں حصہ لینے کے اہل ہوں اور اس میں دلچسپی لینا چاہیں۔ ہم آپ کو دعوت دے رہے ہیں کے آپ تحقیق کے ممبر کے ساتھ ایک انٹرویو میں حصہ لیں یہ جاننے کے لئے کے کیا آپ اس تحقیق کا حصہ بن سکتے ہیں یا نہیں۔ 40 لوگ اس تحقیق میں حصہ لیں گے۔

کیا مجھے حصہ لینا پڑے گا؟

یہ مکمل طور پر آپ پر منحصر ہے کہ آپ شامل ہونے کا فیصلہ کرتے ہیں یا نہیں۔ ہم تحقیق کی وصاحت کریں گے اور اس معلوماتی کتابچے کو دیکھیں گے جو آپ کے پاس ہی رہے گا۔ آپکو آزادی حاصل ہے کہ آپ کسی بھی وقت بنا بتائے تحقیق سے علیحدہ ہو سکتے ہیں۔ اگر آپ شامل نہ ہونے کا فیصلہ کرتے ہیں تو اس کا اثر اس علاج پر نہیں ہو گا جو آپ حاصل کر رہے ہیں۔

اگر میں حصہ لیتا/لیتی ہوں تو میرے ساتھ کیا ہو گا؟

تحقیق کا آغاز:۔

سب سے پہلے آپ تحقیق کے ممبر کے ساتھ انٹرویو میں شامل ہوں گے جس کا مقصد یہ جاننا ہے کے کیا آپ اس تحقیق میں شامل ہونے کے اہل ہیں۔ اگر آپ شامل ہونے کے اہل ہیں اور رضامند ہیں، تو تحقیق کرنے والا کچھ دوسرے معائنے بھی کرے گا جس میں آپ کے میڈیکل اور دوا کے علاج پر موجود کیس نوٹس کا جائزہ لیا جائے گا۔ وہ آپ کے لیئے میڈیکل چیک اپ، خون اور یورین کے معمول کے ٹیسٹ اور بلڈ پریشر کے جائزے کا انتظام کریں گے تا کہ اس بات کا یقین کیا جائے کہ کہیں کوئی ایسی طبی وجہ تو نہیں ہے جس کی وجہ سے آپ کو شرکت نہیں کرنی چاہیے۔ اگر آپ رضامند ہیں، تو ہم آپ کے جی پی سے بھی پوچھیں گے کے وہ آپ کے میڈیکل مسائل کے متعلق ہمیں بتائے۔

اگلی ملاقات میں تحقیق کرنے والا آپ کے نتائج کا معائنہ کرے گا اور اس بات کی تصدیق کرے گا کے آپ تحقیق کو سمجھ چکے ہیں اور جاری رکھنے کے خواہش مند ہیں۔ آپ اپنی علامات کے متعلق کچھ سوالنامے مکمل کریں گے اور آپ کی سوچنے اور غور و فکر کرنے کی صلاحیتوں کے ٹیسٹ ہوں۔ یہ معائنے تحقیق میں بہت زیادہ استعمال کیے جاتے ہیں اور آپ کی اپنی رفتار کے مطابق کیئے جاتے ہیں۔ اس ملاقات پر یا جلد ہی آپ تحقیقی دوا حاصل کریں گے جو آپ معمول کی دوا کے ساتھ کھائیں گے ۔ آپ کے ڈاکٹرز روٹین کے مطابق آپ کو مکمل علاج فراہم کرنا جاری رکھیں گے۔

آپ کا علاج:۔

جو علاج آپ پہلے سے ہی ڈاکٹر سے وصول کر رہے ہیں اس کے ساتھ نیچے دیئے گئے تحقیقی علاج میں سے کوئی ایک علاج اتفاقی طور پر آپکے لیئے مخصوص کر دیا جائے گا؛

مینوسائیکلین، دن میں 1 یا 2 گولیاں فرضی گولیاں، دن میں 1 یا 2 گولیاں

علاج تین مہینے تک جاری رہے گا۔

24 گھنٹوں میں زیادہ سے زیادہ 3 گولیاں لے سکتے ہیں چاہے آپ دن میں ایک دفع لیں یا دن میں دو دفع یا تین دفع، آپ کی پسند کے مطابق ۔ ہمیں معلوم نہیں ہے کے مینوسائیکلین کے فائدے کتنے بڑے ہیں یا یہ کتنی جلدی اثر کرتی ہیں یہ جاننے کے لئے ہمیں فرضی گولیوں کے ساتھ موازنہ کرنے کی ضرورت ہے جو کہ بالکل مینوسائیکلین کی گولیوں کے جیسی ہیں۔ یہ اس لیئے کیا گیا ہے تا کہ کسی کو یہ معلوم نہ ہو سکے کہ اسے کون سی دوا دی جا رہی ہے۔ آپ کے علاج کا انتخاب کمپیوٹر پروگرام کرے گا تا کہ شروع سے ہی اس بات کو یقینی بنایا جائے کہ جو لوگ مینوسائکلین لے رہے ہیں وہ ان کے جیسے ہی ہیں جو کے فرضی دوا لے رہے ہیں ۔ آپ اس بات کا انتخاب نہیں کر سکتے کے آپ کو ان سا علاج حاصل کریں گے۔ نہ ہی آپ کو اور نہ آپ کی کلینیکل ٹیم کو یہ علم ہو گا کے آپ کون سا علاج حاصل کر رہے ہیں کیونکہ آپ کے معائنے کی شناخت کو ڈ نمبر کے ذریعے ہو گی۔ تحقیق کے دوران کسی بھی وقت اگر آپ کسی نقصاندہ اثر کا شکار ہوں تو کوڈ توڑا جا سکتا ہے۔

شروع میں تقریباً 2 ہفتوں کے بعد اور بعد میں ہر 1-2 ماہ بعد تحقیق کرنے والا آپ سے مضر اثرات کے متعلق پوچھے گا/گی۔ کسی پریشانی کی صورت میں آپ کی کلینیکل ٹیم اور تحقیق کرنے والا ہر وقت میسر ہوں گے۔ تحقیقی دوا حاصل کرنے میں ٹیم آپ کی مدد کرے گی۔

فالو۔اپ کی ملاقات:۔

ہم کوشش کے کہ ملاقات کا وقت آپ کے لیے مناسب ہوں اور ایسی جگہوں پر ملاقات کی جائے جو آپ کی ترجیح کے مطابق ہو مثلاً آپ کے گھر کے قریب یا کوئی اور موزوں جگہ۔ ہم دوبارہ 6، 2، اور پھر 12 ہفتوں بعد ملیں گے اور سوالنامے دہرائیں گے اور یہ دیکھیں گے کہ آپ کی زندگی کیسی گزر رہی ہے۔ ہم چرس (cannibas) اور دوسرے نشے کے لئے معمول کے یورین ٹیسٹ کریں گے (pregnancy) کے لئے یوریں ٹیسٹ 1 ماہ کے بعد ہو گا۔ کچھ ملاقاتوں پر ہم خون کا ٹیسٹ بھی دہرائیں گے۔

تحقیقی علاج کا اختتام (3 مہینے)

تحقیقی علاج کا اختتام (3 مہینوں) کے بعد ہو گا جب ہم تمام معائنے دہرائیں گے جو کے شروع میں کیے گئے تھے۔

مجھے کیا کرنا ہو گا؟

تحقیق میں حصہ لینے کے لئے آپ نے جو کرنا ہے اس میں صرف یہ شامل ہے کے آپ تمام ملاقات میں آئیں، معائنہ کرائیں اور تحقیق کے دوران کوئی غیر قانونی مواد نہ کھانے کے لئے رضامند ہوں۔ پر یگننسی pregnancy کے دوران ممکنہ اثرات کی وجہ سے آپ اور جن کے ساتھ آپ سیکس) sex مباشرت) کریں وہ کونٹرا سیپٹو (contraceptive) لینے کے لئے تیار ہوں۔ مرد(condom) اور خواتین contraceptive کی گولی لینے کے لیئے تیار ہوں، ایک IUD ، Spermicidal cream کے ساتھ diaphragm یا اس کا متبادل۔ مزید تفصیلات اس دستاویز کے آخر میں دی گئی ہیں۔

حصہ لینے کے کیا نقصانات اور خطرات ہیں؟

تمام تحقیقی ٹیسٹ اور طریقوں میں ہمارا وسیع تجربہ ہے اور تمام ٹیسٹ بڑی تعداد میں مریضوں کے ساتھ دنیا بھر میں اور یو۔کے میں استعمال ہو رہے ہیں۔ یہ ضروری ہے کے لوگ اسے قابل قبول طریقے سمجھیں۔ تاہم یہ ممکن ہے کے کچھ سوالات آپکو ذاتی، پریشان کن یا تھکا دینے والے لگیں۔ اگر آپ کو ایسا لگے تو ہم اس سے عزت اور ہمدردی کے ساتھ پیش آئیں گے۔ مہاسوں اور دوسرے انفیکشن میں بھی مینو سائیکلین کو استعمال کو کیا جاتا ہے اس لیئے اس بات کے امکان کم ہیں کہ مینو سائیکلین آپکو نقصان پہنچائے۔ کسی بھی دوسری دوا کی طرح ایسا ہو سکتا ہے کہ مینو سائیکلین آپکو سوٹ نہ کرے، مثال کے طور پر اس سے متلی ہو، معدہ خراب یا سر درد ہو۔ اسی طرح آپ ایک جلد کی خارش مبتلا ہو سکتے ہیں۔ بہت کم (10,000 لوگوں میں سے 1 سے بھی کم) ایسا بھی ہوتا ہے کہ جلد کی ایک نسبتاً زیادہ شدید بیماری بھی مینو سائیکلین کی وجہ سے ہو سکتی ہے، جو جلد پر اثر انداز ہو سکتی ہے۔ ہم خاص طور پر اس کے لئے تحقیق کے شروع میں اور اس کے دوران خون کا معائنہ کریں گے تا کہ اسکی جلد پکڑ ہو سکے۔ لمبے علاج میں جلد پر رنگدار مادوں کے ذخیرے تقریباً 2 فیصد لوگوں نے بیان کیے ہیں، اور ہم اس بات کا خیال رکھیں گے کے ہم اس چیز کو ہر ملاقات پر چیک کریں اس سے پہلے کہ یہ ایک مسئلہ بنے آپ دوا لینا بند کر دیں۔

حصہ لینے کے کیا ممکنہ فوائد ہوں گے؟

ہم یہ امید کرتے ہیں کے مینو سائیکلین کا علاج اور معائنہ آپ کے لئے مدد گار ہو گا۔ یہ غالباً بہت جلد عمل نہیں کرتی اس لئے یہ بتانا مشکل ہو سکتا ہے کے یہ آپکو فائدہ دے رہی ہے یا نہیں۔ یہ سوچنے کی کو ئی وجہ نہیں کے یہ آپ کے ڈپریشن کو شدید کر دے گی۔ یہ بتایا گیا ہے کے یہ اینٹی سائیکوٹیک کی وجہ سے بڑھے ہوے وزن کو کم کرتی ہے۔ تاہم، ہم اس کا وعدہ نہیں کر سکتے۔ تحقیق کے اختتام پر جب ہم دو گرہو ں کا موازنہ کریں گے تو ہمارے پاس ایک مضبو ط دلیل ہوگی کہ مینو سائیکلین کو لینا کتنا فائدہ مند ہے اور کیا یہ نئے علاج کی طرف نشاندہی کرتا ہے۔

اگر نئی معلومات حاصل ہو جائیں تو؟

بعض دفع ہم جس علاج پر تحقیق کر رہے ہوتے ہیں اس علاج کے متعلق نئی معلومات حاصل کرتے ہیں۔ اگر ایسا ہو تا ہے تو تحقیقی ٹیم اسکے متعلق آپ سے بات چیت کرے گی۔

کیا میری شمولیت راز میں رکھی جائیگی؟

تحقیق کے دوران آپ کے متعلق جمع کی گئی تمام معلومات سختی سے راز میں رکھی جائیں گی اور ڈیٹا جمع کرنا، محفوظ اور ضائع کرنا 1998 کے ڈیٹا پروٹیکشن ایکٹ (Data Protection Act) کے مطابق ہو گا۔ متعلقہ طبی اور تحقیق سے متعلق دوسرے عوامل کو نوٹ کرنے کے لئے جمع کریں گے۔ ہم آپ کے ٹکات ((notes کے کسی حصے کی فوٹو کاپی نہیں کرائیں گے۔ تحقیقی معلومات کے ساتھ آپکا نام اور پتہ نہیں نوٹ کیا جائے گا ، اس کے برعکس ہم آپ کے تحقیقی ڈیٹا کی شناخت کے لیے ایک کوڈ نمبر استعما ل کریں گے۔

اگر کوئی مسئلہ ہو تو کیا ہو گا؟

اگر تحقیق کے کسی حصے سے متعلق آپ کو کوئی پریشانی ہو، آپ کو تحقیق کرنیوالے سے بات کرنی چاہیے جو آپ کے سوالات کے جواب دینے کی بھرپور کوشش کریں گے۔ (نیچے لکھا گیا نمبر دیکھیں)۔ اگر آپ پھر بھی ناخوش ہوں اور باقاعدہ شکایت کرنا چاہیں تو آپ یہ NHS کے شکایتی طریقہ کار کے ذریعے کر سکتے ہیں۔ تفصیلات ہسپتال سے حاصل کی جاسکتی ہیں۔ اگر آپکے ساتھ کچھ غلط ہو تا ہے اور تحقیق کے دوران آپ کو کوئی نقصان پہنچتا ہے اور ایسا کسی کی غیر ذمہ داری کی وجہ سے ہو تا ہے تو آپ کے پاس مانچسٹر مینٹل ہیلتھ اینڈ سوشل کے ئرٹرسٹ (جنھوں نے اس تحقیق کو لئے فنڈ فراہم کیا ہے) کے تلافی کے قانونی عمل کی بنیاد موجود ہے، لیکن اس کے لئے آپ کو قانونی رقم ادا کرنا پڑے گی۔

اخراجات کا کیا ہو گا؟

کلینک پر ہر تحقیقی ملاقات کے لئے آپ کو سفر کے اخراجات واپس دے ئے جائیں گے۔

Record of Treatment as Usual form

Minocycline as an adjunct treatment for treatment resistant depressive symptoms

MinDep

Follow-up TAU form

Date:..... Researcher Name: .....

Patient ID No: .....

Weight: _____ Waist_____ BP_____ Pulse_____

TAU:

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Hamilton Depression Rating Scale (17-item) – English version

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name

Date of Assessment

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____
0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____
0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

_____
0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

_____
0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
2= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

_____
0= No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Vieweg, The Hamilton rating scale for depression, *Journal of Operational Psychiatry*, 1979;10(2):149-165.

6. INSOMNIA LATE

_____ **0=** No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

_____ **0=** No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____ **0=** Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. AGITATION

_____ **0=** None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

_____ **0=** No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____ **0=** Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____ **0=** None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ **0=** None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ **0=** Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____ **0=** Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

_____ **0=** Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.

_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____ **0=** Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____ **0=** None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____ **0=** Absent
1= Mild
2= Severe

Total Score _____

Presented as a service by

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
Web site: www.glaxowellcome.com

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Hamilton Depression Rating Scale (17-item) – Urdu version

Hamilton Depression Scale (یاسیت کے مرض کے لئے ہیملٹن پیمائشی آلہ)

(صحت کی سہولیات فراہم کرنے والے تربیت یافتہ افراد کے استعمال کے لئے)

مریض کا نام:---------- تاریخ ----------

یہ سوالنامہ ان مریضوں کے لئے ہے جن کے ڈپریشن کے مرض کی تشخیص ہو چکی ہے نتیجہ کے لحاظ سے جتنے زیادہ نمبرز آئیں گے ڈپریشن کی شدت اتنی ہی زیادہ ہوگی۔

ہر علامت کے لئے ذیل میں دیئے گئے نمبر شمار کے مطابق درست نشان لگائیں (ہر علامت کے لئے صرف ایک جواب دیں)

1. افسردگی کی کیفیات (اُداسی، نا اُمیدی، بے چارگی، اپنی اہمیت نہ ہونے کا احساس)

---- 0 = بالکل نہیں

1 = جب پوچھا جائے تو کبھی احساس ہوتا ہے

2 = اکثر بولنے سے ظاہر ہوتی ہیں

3 = بغیر کچھ کہے خیالات دوسروں تک پہنچتے ہیں جیسے (چہرے کے تاثرات، انداز آواز اور رونے کی وجہ سے)

4 = مریض اصل میں یہ احساسات اپنی زبانی اور اپنے انداز سے بتاتا ہے

2. پچھتاوے کے احساسات

---- 0 = بالکل نہیں

1 = اپنے آپ کو الزام دینا کہ آپ کی وجہ سے لوگوں کو نقصان پہنچا ہے

2 = گذشتہ غلطیوں اور گناہ آلود خیالات پر پچھتاوا ہوتا ہے

3 = موجودہ کیفیت میرے گناہوں کی سزا ہے۔

4 = ایسی آوازیں سنائی دیتی ہیں جو ظاہری طور پر آپ کو ڈراتی ہیں

3. خودکشی

---- 0 = بالکل نہیں

1 = زندگی گزارنے کے قابل نہیں رہی

2 = خود سے متعلق ممکنہ موت کے خیالات آتے ہیں اور خواہش ہے کہ مر جاؤں

3 = خودکشی کے خیالات آنا اور اظہار کرنا

4 = خودکشی کرنے کی کوشش کرتے ہیں

4. کم درجے کی بے خوابی (انسومنیا)

---- 0 = سونے میں کوئی مشکل درپیش نہیں ہوتی

1 = کبھی کبھار نیند مشکل سے آتی ہے سونے میں نصف گھنٹہ لگ جاتا ہے

2 = رات میں سونا ہرگز آسان نہیں

1

5. **درمیانے درجے کی بے خوابی (انسومنیا)**

---- 0 = بالکل نہیں

1 = رات کو سونے میں مشکل اور بے چینی ہوتی ہے

2 = رات میں کئی دفعہ سوتے سے اُٹھ جاتے ہیں

6. **انتہائی درجے کی بے خوابی (انسومنیا)**

---- 0 = بالکل نہیں

1 = صبح کے وقت جلدی آنکھ کھل جاتی ہے لیکن پھر دوبارہ نیند آ جاتی ہے

2 = اگر بستر سے اُٹھ جائیں تو نیند آنا مشکل ہوتا ہے

7. **کام کاج کرنے میں مشکلات**

---- 0 = کوئی مشکل نہیں

1 = اپنی نااہلی/معذوری کے احساسات اور خیالات آتے ہیں اور کام کرتے ہوئے ذہن تھک جاتا ہے اور کمزوری کا احساس ہوتا ہے

2 = کام میں دلچسپی ختم ہو جاتی ہے مریض خود بتاتا ہے یا پھر اکثر آپ اسے خود محسوس کرتے ہیں فیصلہ کرنے میں پس وپیش سے کام لیتا ہے (ایسے محسوس ہوتا ہے کہ وہ زبردستی کام کر رہا ہے)

3 = آپ کی کارکردگی اور نتائج میں خاطر خواہ کمی محسوس ہوتی ہے

4 = موجودہ کیفیت کی وجہ سے کام ہی نہیں کرتے

8. **سوچنے، بولنے اور توجہ دینے میں مشکلات**

---- 0 = نارمل بول چال اور خیالات

1 = انٹرویو کے وقت تھوڑی مشکلات درپیش ہوتی ہیں

2 = انٹرویو کے وقت زیادہ مشکلات درپیش ہوتی ہیں

3 = انٹرویو مشکل چیز ہے

4 = انٹرویو بالکل نہیں دے سکتی

9. **بے چینی**

---- 0 = بالکل نہیں

1 = تھوڑی بہت بے چینی ہونا

2 = ہاتھوں یا بالوں کے ساتھ کھیلنا شروع کر دیتے ہیں

3 = بیٹھا نہیں جاتا ٹہلنا شروع کر دیتا ہوں

4 = ہاتھوں کو مروڑنا، ناخن چبانا/کاٹنا/بال کھینچنا، ہونٹوں کا کاٹنا

10. **تشویش (نفسیاتی)**

---- 0 = بالکل نہیں

1 = پریشانی (کھینچاؤ) اور بے چینی

2 = چھوٹی چھوٹی باتوں کے بارے میں سوچتا ہوں

3 = میری پریشانی چہرے اور باتوں میں ظاہر ہو جاتی ہے

4 = بغیر پوچھے اپنے ڈر کا اظہار کرنا

11. **جسمانی تشویش/اندیشہ:** جسمانی طور پر تشویش کا لازمی ہونا

(جیسے خود اختیاری نظام کا زیادہ کام کرنا، کھانا ہضم نہ ہونا، معدے میں بل پڑنا، ڈائیریا، نبض کا تیز ہو جانا، پسینے آنا، جسم کا نپنا، سر میں درد، پیشاب بکثرت آنا وغیرہ) ۔ادویات کے نتیجے میں پیدا ہونے والے امراض کے بارے میں نہیں پوچھا جائے (جیسے منہ کا خشک ہونا، قبض ہونا)

---- 0 = بالکل نہیں

1 = تھوڑا بہت

2 = درمیانے درجے کا

3 = شدید

4 = برداشت سے باہر

12. **جسمانی علامات (نظام انہضام)**

---- 0 = نہیں

1 = بھوک کا خاتمہ، لیکن دوسروں کے کہے بغیر کھانا کھا لینا۔ تقریباً نارمل خوراک لینا۔

2 = بغیر کسی کے کہے کھانا کھانے میں مشکل پیش آنا۔ بھوک اور خوراک کی طلب میں شدید کمی واقع ہونا۔

13. **عام جسمانی علامات**

---- 0 = بالکل نہیں

1 = بازو، ٹانگوں، کمر یا سر میں بھاری پن ہونا، کمر میں درد، سر میں درد، جوڑوں میں درد، توانائی کا ختم ہونا اور تھکان

2 = کوئی بھی واضح علامت

14. **اعضائے مخصوصہ سے متعلق علامات** (علامات جیسے کہ: جنسی خواہش کا ختم ہونا، جنسی عمل کی کمزوری، ماہواری میں بے قاعدگی)

---- 0 = نہیں (غیر حاضر)

1 = درمیانہ

2 = شدید

15. **جسمانی صحت کے بارے میں وہم (مراق)**

---- 0 = نہیں ہے

1 = خودساختہ علامات (جسمانی)

2 = صحت کے متعلق زیادہ سوچ وفکر

3 = صحت سے متعلق جلدی جلدی شکایت، مدد کے لئے درخواست، وغیرہ

4 = جسمانی صحت سے متعلق غلط اور بے بنیاد یقین

16. **وزن میں کمی واقع ہونا** (بیماری کا پس منظر دیکھتے ہوئے)

---- 0 = وزن کی کمی نہیں

1 = ممکنہ طور پر موجودہ بیماری کی وجہ سے وزن میں کمی واقع ہونا

2 = یقیناً (مریض کے مطابق) وزن میں کمی واقع ہونا

3 = کبھی تعین انہیں کیا

17. **بصیرت (بیماری کا شعور)**

---- 0 = بیماری اور اُداسی کی بیماری کو ماننا یا شعور رکھنا

1 = اقرار کرنا مگر ناقص خوراک، آب وہوا، کام کی زیادتی، وائرس، آرام کی تلاش وغیرہ کو ذمہ دار قرار دینا

2 = بیماری سے انکار کرنا

18. **روزمرہ کا اتار چڑھاؤ**

A ۔ نوٹ کریں کہ یہ علامات صبح میں زیادہ خراب ہوتی ہیں یا شام میں: اگر روزمرہ کا اتار چڑھاؤ نہیں ہے تو نہیں پر نشان لگائیں

---- 0 = کوئی تبدیلی نہیں ہوتی

1 = صبح کے وقت

2 = شام کے وقت

B ۔ اگر تبدیلی ہے تو اس کی شدت کس حد تک ہے۔ اگر تبدیلی نہیں ہے تو نہیں پر نشان لگائیں

---- 0 = نہیں

1 = درمیانی حد تک

2 = شدید حد تک

19. **شخصی وجود کا احساس ختم ہوجانا** (غیر حقیقی سوچیں؛ غیر حقیقت پسندانہ سوچ)

---- 0 = نہیں ہے

1 = تھوڑا بہت

2 = درمیانی حد تک

3 = شدید حد تک

4 = ناقابل برداشت

20. **شک وشبہ سے متعلق علامات**

---- 0 = نہیں

1 = شک وشبہ

2 = خیالات کے حوالے تلاش کرنا

3 = دوسروں کے متعلق انتقامی اور جارحیت پر مبنی اوہام پیدا ہونا

21. **وہم سے متعلق علامات**

---- 0 = نہیں

1 = درمیانے درجے کی

2 = شدید

Patient Health Questionnaire (PHQ-9) – English and Urdu version

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day).

گزشتہ 2 ہفتوں کے دوران آپ کو درج ذیل مسائل کی وجہ سے کتنی مرتبہ مشکل پیش آئی؟

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	خانے میں اپنے جواب کی نشاندہی کے لئے "درست" کا نشان لگائیں	بالکل نہیں (0) Not at all	کئی دن (1) Several days	آدھے دن سے زیادہ (2) More than half the days	تقریباً روزانہ (3) Nearly every day
1	کچھ بھی کرنے میں بہت کم دلچسپی یا خوشی ہوتی ہے۔ Little interest or pleasure in doing things				
2	پژمردہ، افسردہ یا ناُمید ہونا Feeling down, depressed, or hopeless				
3	سونے یا سوئے رہنے میں مشکل ہونا، یا بہت زیادہ سونا Trouble falling or staying asleep, or sleeping too much				
4	تھکان محسوس کرنا یا بہت کم توانائی محسوس کرنا Feeling tired or having little energy				
5	بھوک میں کمی یا بہت زیادہ کھانا Poor appetite or overeating				
6	اپنے متعلق بُرا محسوس کرنا۔ یا یہ کہ آپ ناکارہ ہیں یا آپ نے خود کو یا اپنے خاندان کو مایوس کیا ہے Feeling bad about yourself - or that you are a failure or have let yourself or your family down?				
7	کسی کام میں توجہ مرکوز کرنے میں مشکل ہونا، جیسے کہ اخبار پڑھنا یا ٹی وی دیکھنا Trouble concentrating on things, such as reading the newspaper or watching television?				
8	اتنا آہستہ حرکت یا بات کرنا جسے دوسرے لوگ محسوس کر سکتے تھے؟ یا اس کا الٹ، اتنی بے چینی محسوس کرنا کہ آپ معمول سے زیادہ حرکت کریں Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?				
9	اس قسم کے خیالات آنا کہ آپ کا مر جانا ہی بہتر ہے یا خود کو کسی طریقے سے تکلیف پہنچانے کے بارے میں سوچنا Thoughts that you would be better off dead, or of hurting yourself in some way?				
	ٹوٹل اسکور Total Score	/ 27			

اگر آپ نے مذکورہ بالا مسائل پر نشان لگائے ہیں تو ان مسائل نے آپ کے کام کرنے، گھر میں صورت حال سے نمٹنے، یا دوسرے لوگوں کے ساتھ تعلقات رکھنے کو کتنا مشکل بنایا ہے۔

If you checked off any problems, how difficult have these problems made it for you to do your workm take care of things at home, or get along with other people

بالکل مشکل نہیں بنایا ہے No difficult at all	کچھ حد تک مشکل بنایا ہے Some what difficult	بہت مشکل بنایا ہے Very difficult	حد سے زیادہ مشکل بنایا ہے Extremely difficult

Generalised Anxiety Disorder-7 rating scale (GAD-7) - English and Urdu version

G A D - 7

گزشتہ 2 ہفتوں کے دوران آپ کو درج ذیل مسائل کی وجہ سے کتنی مرتبہ مشکل پیش آئی ؟

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	خانے میں اپنے جواب کی نشاندہی کے لئے "درست" کا نشان لگائیں	بالکل نہیں(0) Not at all sure	کئی دن(1) Several days	آدھے دن سے زیادہ(2) More than half the days	تقریباً روزانہ (3) Nearly every day
1	حواس باختہ، مضطرب یا بے بس محسوس کرنا۔ Feeling nervous, anxious, or on edge				
2	فکر کرنا بند نہ کرنا یا پر قابو نہ پانا Not being able to stop or control worrying				
3	مختلف چیزوں کے بارے میں بہت زیادہ فکر کرنا Worrying too much about different things				
4	سستانے میں مشکل محسوس کرنا Trouble relaxing				
5	اتنا بے چین محسوس کرنا کہ ایک جگہ بیٹھنا مشکل ہو Being so restless that it's hard to sit still				
6	بہت آسانی سے ناراض یا غصہ ہو جانا Becoming easily annoyed or irritable				
7	یہ ڈر محسوس کرنا کہ کچھ برا ہونے والا ہے Feeling afraid as if something awful might happen				
	Add the score for each column تمام کالم کے اسکور کو جمع کریں				
	Total Score (add your column scores) =				

as "0" (not at all) to "3" (nearly every day).

Clinical Global Impression scale

Clinical Global Impression Scale (CGI)

Patient ID_____

Severity of illness:

Considering your total clinical experience with particular population, how mentally ill is the patient at this time?

0 Not assessed

1 Normal, Not Ill at ell

2 Borderline Mentally Ill

3 Mildly ill

4 Moderately Ill

5 Markedly Ill

6 Severely Ill

7 Among the most extremely ill of subjects

EuroQoL EQ-5D rating scale – English and Urdu version

EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

مندرجہ ذیل ہر گروپ کے کسی ایک خانے پر درست / صحیح کا نشان لگائیں۔برائے مہربانی ان جملوں کو ظاہر /نشاندہی کریں جو آپ کی آج کل کی صحت کی بہترین عکاسی کرتے ہیں۔

1. **Mobility چلنا پھرنا / حرکت / تحریک**	
I have no problems in walking about مجھے چلنے پھرنے میں کوئی مشکل نہیں	☐
I have some problems in walking about مجھے چلنے پھرنے میں کچھ مشکل ہوتی ہے	☐
I am confined to bed میں بالکل چل پھر نہیں سکتا/سکتی	☐

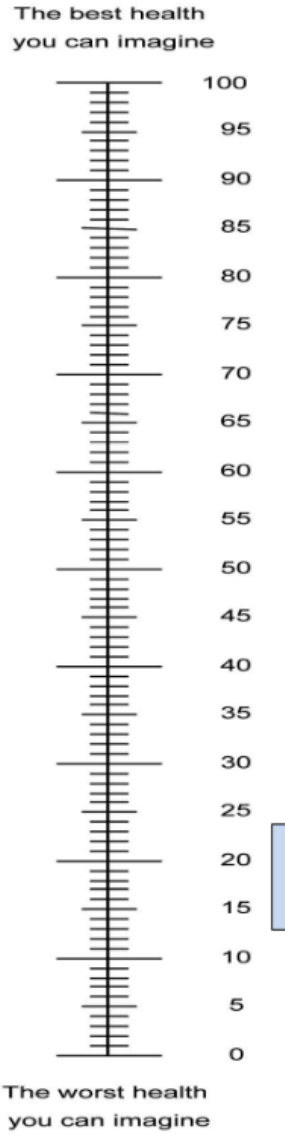
2. **Self-Care اپنی دیکھ بھال / نگہداشت**	
I have no problems with self-care مجھے اپنی دیکھ بھال کرنے میں کوئی مشکل نہیں	☐
I have some problems washing or dressing myself مجھے نہانے اور کپڑے پہننے میں کچھ مشکل ہوتی ہے	☐
I am unable to wash or dress myself میں خود نہا یا کپڑے نہیں پہن سکتا /سکتی	☐

3. **Usual Activities (e.g. work, study, housework, family or leisure activities)** **روزمرہ کے معمولات** (مثلاً کام، پڑھائی، گھریلو کام کاج،خاندانی اور تفریحی مصروفیات)	
I have no problems with performing my usual activities مجھے اپنے روزمرہ کے کام کاج میں کوئی مشکل نہیں ہوتی	☐
I have some problems with performing my usual activities مجھے اپنے روزمرہ کے کام کاج میں کچھ مشکل ہوتی ہے	☐
I am unable to perform my usual activities میں اپنے روزمرہ کے کام کاج نہیں کرسکتا/سکتی	☐

4. **Pain/Discomfort درد / بے آرامی**	
I have no pain or discomfort مجھے کوئی درد یا بے آرامی نہیں	☐
I have moderate pain or discomfort مجھے کچھ درد یا بے آرامی ہے	☐
I have extreme pain or discomfort مجھے شدید درد یا بے آرامی ہے	☐

5. **Anxiety/Depression بے چینی /ذہنی پریشانی (ڈپریشن)**	
I am not anxious or depressed مجھے کوئی بے چینی یا ذہنی پریشانی نہیں ہے	☐
I am moderately anxious or depressed مجھے کچھ بے چینی یا ذہنی پریشانی ہے	☐
I am extremely anxious or depressed مجھے شدید بے چینی یا ذہنی پریشانی ہے	☐

EQ-5D Visual Analogue Scale (VAS) – English and Urdu version



We would like to know how good or bad your health is **TODAY.**

This scale is numbered from **0** to **100**, **100** means the best health you can imagine, **0** means the worst health you can imagine. Mark an **X** on the scale to indicate how your health is **TODAY**. Now, please write the number you marked on the scale in the box below.

اپنی حالیہ صحت کی صحیح طور پر نشاندہی کرنے کے لئے ہم نے آپ کی آسانی کےلئےایک(تھرما میٹر کی طرح) پیمانہ بنایا ہے۔ اس پیمانے پر سو **(100)** آپ کی بہترین اور صفر **(0)** آپ کی بدترین صحت کی نشاندہی کرتا ہے۔
ہم چاہیں گے کہ آپ اس پیمانے پر نشاندہی کریں کہ آج کل آپ کے خیال میں آپ کی صحت کیسی ہے (بہترین یا بدترین)
نیچے دیئے گئے (آپ کی موجودہ صحت) خانے سے ایک لائن لگائیں جو پیمانے پر موجود اس نشان تک ہو جو آپ کی موجودہ صحت کی صحیح نشاندہی کرتی ہو۔

Your own health state today

آپ کی موجودہ صحت

Side Effect Checklist

Side effects check for Minocycline

Center ID_____ Participant ID:_____Date:_____

Followup No: _____Name of Researcher:_____

NAME	YES	NO
Nausea		
Vomitting		
Diarrhea		
Dysphagia		
Esophageal irritation		
Anorexia		
Dizziness		
Tinnitis		
Vertigo		
Headache		
Visual disturbances		
Hepatotoxicity		
Pancreatitis		
Antibiotic associated colitis		
Blood dyscrasias		
Photosensitivity		
Teeth discoloration		
Skin discoloration		
Conjunctival, sweat and tear discoloration		
Dark furry tongue, black or swollen tongue		
Exacerbation of SLE		
Exacerbation of Myesthenia Gravis		
Vaginal yeast infection		
Hypersensitivity reactions:		
* rash		
* urticaria		
* angioedema		
* anaphylaxis		

* pericarditis		
exfoliative dermatitis		

Mini International Neuropsychiatric Interview (MINI) (Urdu version)

منی پلس

M.I.N.I. PLUS

منی بین الاقوامی اعصابی و نفسیاتی انٹرویو

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

اردو ورژن منی پلس ۵

Urdu Version 5.0.0

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Patient Name:		*Patient Number:*	
Date of Birth:		*Time Interview Began:*	
Interviewer's Name:		*Time Interview Ended:*	
Date of Interview:		*Total Time:*	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Recurrent	☐ ☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
	MDE WITH MELANCHOLIC FEATURES Optional	Current (2 weeks)	☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1
C	SUICIDALITY	Current (Past Month) Risk: ☐ Low ☐ Medium ☐ High	☐		
D	MANIC EPISODE	Current Past	☐ ☐	296.00-296.06	F30.x-F31.9
	HYPOMANIC EPISODE	Current Past	☐ ☐	296.80-296.89	F31.8-F31.9/F34.0
E	PANIC DISORDER	Current (Past Month) Lifetime	☐ ☐	300.01/300.21	F40.01-F41.0
F	AGORAPHOBIA	Current	☐	300.22	F40.00
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8
I	POSTTRAUMATIC STRESS DISORDER Optional	Current (Past Month)	☐	309.81	F43.1
J	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Past 12 Months Past 12 Months	☐ ☐	303.9 305.00	F10.2x F10.1
K	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months	☐ ☐	304.00-.90/305.20-.90 304.00-.90/305.20-.90	F11.1-F19.1 F11.1-F19.1
L	PSYCHOTIC DISORDERS	Lifetime Current	☐ ☐	295.10-295.90/297.1/ 297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current	☐	296.24	F32.3/F33.3
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0
O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.
•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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"مینی سکرین" (Mini Screen)

نمبر شمار				متعلقہ حصہ
1	کیا پچھلے دو ہفتوں میں تقریباً روزانہ یا دن کے زیادہ حصے میں آپ لگاتار اداس یا غمگین رہے؟	نہیں	ہاں	A
2	کیا پچھلے دو ہفتوں میں آپکی دلچسپی زیادہ تر چیزوں میں کم ہو گئی ہے یا جن چیزوں سے آپ پہلے لطف اندوز ہوتے تھے اب ان میں کم مزہ آتا ہے؟	نہیں	ہاں *	A
3	کیا آپ پچھلے دو سالوں میں زیادہ تر وقت اداس یا غمگین رہے؟	نہیں	ہاں	B
4	پچھلے مہینے میں کیا آپ کے دل میں موت کی خواہش پیدا ہوئی، یا آپ نے سوچا کہ اس زندگی سے تو موت بہتر ہے؟	نہیں	ہاں	C
5	کبھی بھی آپ کی زندگی میں کوئی ایسا وقت گزرا جب: آپ بہت زیادہ خوش رہے ہوں۔ یا (بہت زیادہ کام کرنے لگے ہوں) آپ میں بہت زیادہ طاقت اور توانائی آگئی ہو۔ جس کے نتیجے میں آپ نے اپنے لیے مشکلات پیدا کر لی ہوں۔ یا دوسرے لوگوں کا یہ خیال ہے کہ آپ میں کوئی تبدیلی آگئی ہے۔ (کسی نشے / شراب کے بغیر)؟	نہیں	ہاں	D
6	کیا کبھی ایسا ہوا کہ آپ لگاتار کئی دن چڑچڑے پن کا شکار رہے ہوں یہاں تک کہ گھر سے باہر لوگوں سے آپ کی تکرار (تو تو، میں میں) ہو گئی ہو یا جھگڑا اور لڑائی تک نوبت آگئی ہو یا آپ نے کسی کو برا بھلا کہا ہو؟	نہیں	ہاں	D
7	کیا آپ کو یا دوسرے لوگوں کو لگا کہ آپ عام لوگوں کی نسبت زیادہ چڑچڑے یا غصیلے ہو گئے ہیں۔ چاہے آپ ان صورتوں میں حق بجانب ہی کیوں نہ تھے؟۔	نہیں	ہاں	D
8	کیا آپ پر ایک یا ایک سے زیادہ دفعہ کوئی ایسی کیفیت طاری ہوئی کہ آپ کو اچانک گھبراہٹ، خوف یا بے چینی محسوس ہونے لگی جب کہ دوسرے لوگ ایسی حالت میں اسطرح محسوس نہیں کرتے؟ کیا یہ دورہ یا کیفیت ۱۵ منٹ میں اپنی انتہا کو پہنچ گئی؟۔	نہیں	ہاں	E

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9	کیا ہجوم یا قطار میں کھڑے ہوئے، گھر سے دور یا گھر پہ اکیلے میں یا پل سے گزرتے ہوئے یا بس ویگن، گاڑی وغیرہ میں جہاں سے آپ آسانی سے نہ نکل سکتے ہوں اور آپ کی مدد کے لیے کوئی موجود نہ ہو، تو آپ کو یہ گھبراہٹ یا بے آرامی ہو جاتی ہے کہ آپ کو گھبراہٹ کا دورہ پڑ جائے گا یا گھبراہٹ کی طرح کی علامات جن کا ہم نے ذکر کیا ہونے لگیں؟	نہیں	ہاں	F
10	پچھلے مہینے میں کیا آپ کو یہ فکر یا اندیشہ تو نہیں تھا کہ لوگ آپ کو دیکھ رہے ہیں۔ آپ لوگوں کی توجہ کا مرکز ہیں۔ یا یہ کہ لوگ آپ کی تذلیل کریں گے۔ مثلاً جب آپ لوگوں کے سامنے باتیں کر رہے ہوں یا ہر مجمع (جیسے شادی بیاہ، ہوٹل وغیرہ) میں کھانا کھاتے ہوئے یا کسی کے سامنے لکھ رہے ہوں یا ویسے ہی لوگوں کے درمیان ہوں؟۔	نہیں	ہاں	G
11	کیا پچھلے ماہ کے دوران آپ کو کوئی خاص وسوسہ یا کچھ کرنے کا خیال یا ذہن میں کوئی تصور اگر بار بار ستاتا رہا ہے۔ جو آپ کی مرضی کے خلاف ہو، ناخوشگوار ہو، غیر مناسب ہو اور وہ آپ کے اندر گھر کر گیا ہو۔ مثلاً یہ خیال کہ آپ صاف یا پاک نہیں ہیں۔ آپ کو جراثیم لگ گئے ہیں یا لگ جائیں گے۔ یا آپ کسی کو نا چاہتے ہوئے نقصان پہنچا دیں گے یا یہ خوف کہ آپ کچھ کر بیٹھیں گے۔ یا یہ وہم کہ آپ سے کام بگڑ جائیں گے۔ یا جنسی نوعیت کے خیالات، تصور یا خواہش، یا چیزیں جمع کرنا، یا مذہبی وسوسے وغیرہ؟۔	نہیں	ہاں	H
12	پچھلے مہینے کے دوران کیا آپ کو کئی کام بار بار کرنا پڑے اور آپ نے روکنے کی کوشش کی ہو مگر مجبور ہو گئے ہوں جیسے ہاتھوں کو بار بار دھونا یا صفائی کرنا یا گننا یا چیزوں کو بار بار چیک کرنا چیزوں کو اکٹھا کرنا یا خاص ترتیب سے رکھنا یا کوئی دوسرا اسی طرح کا معمول؟	نہیں	ہاں	H
13	کیا کبھی آپ نے کوئی ایسا واقعہ دیکھا یا آپ کو درپیش آیا جو کہ ہولناک ہو، جس میں کسی کی جان چلی گئی ہو، یا ایسا ہونے کا شدید امکان ہو؟ آپ یا پھر کوئی اور شدید زخمی ہو گیا ہو، مثلاً کوئی بڑا حادثہ، جنسی یا جسمانی حملہ، دہشت گردی کا واقعہ یا کسی کو یرغمال بنا لیا گیا ہو یا کہیں آگ لگ گئی ہو؟ کوئی لاش دیکھی ہو؟ کسی عزیز دوست کی اچانک موت، جنگ یا کوئی قدرتی آفت وغیرہ؟۔	نہیں	ہاں	I
14	کیا آپ نے اس واقعے سے شدید خوف، بے بسی اور دہشت محسوس کی؟	نہیں	ہاں	I
15	کیا پچھلے ماہ کے دوران یہ واقعہ پھر اگر آپ کو ستاتا رہا ہے؟ جیسے ڈراونے خواب یا خیال کی صورت	نہیں	ہاں	I

	میں یا اس کی کوئی جھلک، یا جسمانی علامات؟۔			
16	کیا پچھلے 22 ماہ میں آپ نے تین سے زیادہ مرتبہ تین گھنٹے کے اندر اندر تین یا زیادہ شراب کے گلاس پیئے ہیں؟۔	نہیں	ہاں	J
17	اب میں آپ کو کچھ نشہ آور چیزوں اور دواؤں کی فہرست دکھانے لگا رہا ہوں۔ آپ پڑھ کر بتائیں کہ کیا پچھلے بارہ ماہ کے دوران آپ نے کبھی ایک سے زیادہ مرتبہ تازہ دم ہونے یا اچھا محسوس کرنے کی خاطر، یا اپنے موڈ کی تبدیلی کے لیے ان میں سے کسی کا استعمال کیا ہے؟۔ ایمفٹامین، سپیڈ، کرسٹل میتھ، ڈکسڈرین، ریٹالین، کوکین، کریک، فری بیس، ڈائیٹ پلز، ہیروئن، مورفین میتھا ڈون، اوپیم (افیم)، ڈیمرول، کوڈین، پرکوڈان، آکسی کونین، ایل ایس ڈی، میسکنین، پی	نہیں	ہاں	K
18	کیا کبھی آپ کو اس بات کا یقین ہوا کہ لوگ آپ کی جاسوسی کر رہے ہیں یا کوئی آپ کے خلاف سازش کر رہا ہے یا آپ کو نقصان پہنچانے کی کوشش کر رہا ہے؟ اگر 'ہاں' تو (مثالوں سے پتہ چلائیں کہ حقیقت کیا ہے)			L
19	پچھلے ماہ میں آپ کا وزن کم سے کم کتنا تھا؟ ----/----/----/---- پونڈ			
20	کیا مریض کا وزن اس کے قد کے مطابق وزن سے کم ہے؟ نوٹ:۔ (وزن کا چارٹ صفحہ نمبر ۲۸)	نہیں	ہاں	M
21	کیا ایسا ہوا کہ پچھلے تین ماہ میں آپ نے کئی دفعہ اکٹھا بہت زیادہ کھانا کھا لیا ہو، یا دو گھنٹے کے اندر اندر بہت زیادہ مقدار میں کھایا ہو؟	نہیں	ہاں	N
22	پچھلے تین ماہ میں کیا ایسا ایک ہفتے میں دو سے زیادہ مرتبہ ہوا؟	نہیں	ہاں	N
23	پچھلے چھ ماہ کے دوران آپ زیادہ فکر مند رہے ہوں۔ یا بہت زیادہ چیزیں آپ کو پریشان کرتی رہی ہوں؟	نہیں	ہاں	O

نوٹ:۔ اگر کسی سوال کا جواب ہاں میں ہو تو اسکے متعلقہ حصہ پر جائیں۔

MAJOR DEPRESSIVE EPISODE اداسی کا بڑا دورہ (A)

A1	کیا آپ پچھلے دو ہفتوں کے دوران ہر روز یا دن کا زیادہ تر حصہ مسلسل اداس یا غمگین رہے؟	نہیں	ہاں	1
A2	کیا پچھلے دو ہفتوں میں آپ کی زیادہ تر چیزوں میں دلچسپی کم ہوگئی تھی یا جن چیزوں میں آپ کو اکثر اوقات مزہ آتا تھا ان میں اب آپ کو کم مزہ آتا ہے؟ کیا پہلے دونوں کوڈز کا جواب "ہاں" ہے؟	نہیں ← نہیں	ہاں* ہاں	2
A3	پچھلے دو ہفتوں میں جب آپ اداس تھے یا آپ کی دلچسپی کم ہوگئی تھی تو:			
a	آپ کی بھوک کم یا زیادہ ہوئی؟ اور کیا ایسا تقریباً روزانہ ہوا؟ کیا آپ کا وزن کسی کوشش کے بغیر کم یا زیادہ ہوگیا؟	نہیں	ہاں	3
b	کیا آپ کو تقریباً روزانہ رات کو سونے میں مشکلات کا سامنا کرنا پڑتا ہے؟	نہیں	ہاں	4
c	کیا آپ پہلے کے مقابلے میں زیادہ سست رفتاری سے بولتے اور حرکت کرتے ہیں؟	نہیں	ہاں*	5
d	کیا تقریباً روزانہ آپ تھکاوٹ محسوس کرنے لگے ہیں یا آپ کی توانائی کم یا ختم ہوگئی ہے؟	نہیں	ہاں	6
e	کیا آپ اپنے آپ کو تقریباً روزانہ بالکل بے وقعت یا گنہگار محسوس کرنے لگے ہیں؟	نہیں	ہاں	7
f	کیا آپ کے لیے تقریباً روزانہ کسی چیز پر توجہ مرکوز کرنا یا فیصلہ کرنا مشکل ہوگیا ہے؟	نہیں	ہاں	8
g	کیا آپ کے ذہن میں متواتر اپنے آپ کو نقصان پہنچانے، یا اپنی زندگی ختم کرنے یا موت کی خواہش جیسے خیالات آتے ہیں؟	نہیں	ہاں	9

کیا A1- A3 کے پانچ یا اس سے زیادہ کے جوابات ہاں میں ہیں؟

نہیں	ہاں*
اداسی کا بڑا دورہ، موجودہ	

اگر مریض کو "اداسی کا بڑا دورہ، موجودہ ہے تو A4 کو جاری رکھیں، ورنہ ماڈل B پر چلے جائیں۔

A4 (a	کیا ماضی میں آپ کی زندگی میں (اس دفعہ کے علاوہ بھی) دو ہفتے کا عرصہ یا عرصے آئے ہیں جب آپ اداس رہے ہوں یا اکثر چیزوں میں آپ کی دلچسپی کم ہوگئی ہو یا آپ کو ان مشکلات میں سے اکثر کا سامنا رہا ہے جن کے متعلق ہم نے ابھی گفتگو کی ہے۔	نہیں ←	ہاں	10
(b	اداسی کی بیماری کے دوران کیا کبھی ایسا ہوا کہ دو ماہ کے لیے آپ بالکل ٹھیک ہوگئے اور آپکو اداسی اور دلچسپی کے کم ہونے جیسا کوئی مسئلہ نہ رہا؟	نہیں ہاں اداسی کا پرا دورہ، مکرر		11

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اداسی کا بڑا دورہ، میلنخولیا کی خصوصیات سمیت (اختیاری)

(Major Depressive Episode with Melancholic Features) (Optional)

←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔

اگر مریض کا اداسی کے بڑے دورے، موجودہ (A3) پر جواب "ہاں" ہے تو درج ذیل سوالات پوچھیں۔

A5 (a)	کیا A2 کا جواب "ہاں" ہے؟	نہیں	ہاں	
(b)	موجودہ اداسی کا دورہ جب شدید تھا تو کیا ایسا ہوا کہ آپ ان چیزوں سے بھی مزہ یا خوشی حاصل نہیں کر پائے جن سے آپ کو پہلے مزہ یا خوشی ملتی تھی؟ اگر نہیں: تو کیا آپ کسی اچھی یا خوشی کی بات پر وقتی طور پر بہتر محسوس کرتے ہیں۔	نہیں	ہاں	12
	کیا A5b اور A5a میں کسی کا جواب "ہاں" ہے؟	نہیں	ہاں	
A6	پچھلے دو ہفتوں کے دوران جب آپ نے مایوسی اور اداسی محسوس کی:			
a	کیا یہ اداسی اس سے مختلف تھی جس کا تجربہ آپ کو کسی دوست یا عزیز کی وفات پر ہوا؟	نہیں	ہاں	13
b	کیا آپ کی طبیعت تقریباً روزانہ اور متواتر صبح کے وقت خراب رہتی تھی؟	نہیں	ہاں	14
c	کیا تقریباً روزانہ آپ (اپنی عادت کے خلاف) دو گھنٹے پہلے بیدار ہو جاتے تھے اور دوبارہ سونے میں مشکل پیش آتی تھی؟	نہیں	ہاں	15
d	کیا A3c کا جواب "ہاں" ہے؟ (Psychomotor retardation or agitation)	نہیں	ہاں	
e	کیا A3a کا جواب "ہاں" ہے؟ (For Anorexia or weight loss)	نہیں	ہاں	16
f	کیا آپ نے بہت زیادہ احساس جرم یا گناہ محسوس کیا؟ جو حقیقی صورت حال کے مقابلے میں غیر متناسب تھا؟	نہیں	ہاں	
	کیا A6 کے تین یا تین سے زیادہ جواب "ہاں" ہیں؟	نہیں اداسی کا بڑا دورہ، میلنخولیا کی موجودہ خصوصیات سمیت	ہاں	

لمبے عرصے کی اداسی (B. DYSTHYMIA)

←Diagnosisپر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Moduleپر چلے جائیں۔

اگر مریض کی علامات اداسی کے بڑے دورے، موجودہ کے معیار کے مطابق ہیں تو اس یہ سوالات نہ پوچھیں۔

نمبر شمار				
B1	کیا آپ پچھلے دو سالوں میں زیادہ تر مایوس اور اداس رہے؟	نہیں←	ہاں	17
B2	کیا اس دوران کوئی دو ماہ یا اس سے زیادہ مدت کا عرصہ ایسا آیا جب آپ نے بہتر محسوس کیا ہو؟	نہیں	ہاں←	18
B3	کیا اداسی کی اس مدت کے دوران اکثر اوقات: 2- آپ کی بھوک میں نمایاں تبدیلی آئی ہو؟	نہیں	ہاں	19
	2- کیا آپ کو سونے میں مشکل ہونے لگی ہو یا آپ زیادہ سونے لگے ہوں؟	نہیں	ہاں	20
	3- کیا آپ تھکاوٹ یا کمزوری محسوس کرنے لگے ہیں؟	نہیں	ہاں	21
	4- کیا آپ میں اعتمادی کی کمی ہے؟	نہیں	ہاں	22
	5- کیا آپ کو توجہ مرکوز کرنے یا کوئی فیصلہ کرنے میں کوئی مشکل پیش آئی؟	نہیں	ہاں	23
	6- کیا آپ مایوس اور نا امید رہنے لگے؟	نہیں	ہاں	24
	7- کیا B3 میں دو یا دو سے زائد جوابات "ہاں" ہیں؟	نہیں←	ہاں	
B4	کیا اداسی کی ان علامات کے نتیجے میں آپ کو کافی تکلیف ہوئی۔ اداسی کی علامات کی وجہ سے آپ کے کام کرنے کی صلاحیت اور میل جول یا کسی اور پہلو پر اثر پڑا؟	نہیں←	ہاں	25
	کیا B4 کا جواب ہاں میں ہے؟			

نہیں	ہاں
لمبے عرصے کی اداسی	
موجودہ	

خودکشی کے خیالات (C. SUICDALITY)

C1	کیا پچھلے مہینے میں آپ نے: موت کی خواہش کی یا یہ سوچا کہ اس زندگی سے موت بہتر ہے؟	نہیں	ہاں	1
C2	آپنے آپ کو نقصان پہنچانا چاہا؟	نہیں	ہاں	2
C3	خودکشی کے بارے میں سوچا؟	نہیں	ہاں	6
C4	خودکشی کا کوئی منصوبہ بنایا؟	نہیں	ہاں	10
C5	خودکشی کی کوشش کی؟	نہیں	ہاں	10
C6	کیا آپ نے اپنی زندگی میں کبھی بھی خودکشی کی کوشش کی ہے؟	نہیں	ہاں	4

کیا مندرجہ بالا سوالات میں کسی ایک کا جواب بھی "ہاں" ہے؟

اگر جواب "ہاں" ہے تو C1-C6 کے سکورز کو جمع کریں اور خودکشی کے رجحان کی اس طرح سے پیمائش کریں۔

نہیں	ہاں
خودکشی کا موجودہ خطرہ	
Low	**1-5 Points**
Moderate	**6-9 Points**
High	**≥10 Points**

D. (HYPO) Manic Episode مینیا کا ہلکا دورہ

←Diagnosisپر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Moduleپر چلے جائیں۔

D1 (a)	کیا کبھی بھی آپ کی زندگی میں ایسا وقت آیا جب؛ آپ خوشی یا موج کی حالت میں رہے ہوں یا آپ میں بہت طاقت آگئی ہو یا آپ خود کو کوئی بڑی چیز سمجھنے لگے ہوں جس سے آپ نے اپنے لیے مشکلات پیدا کرلی ہوں یا دوسرے لوگوں کا خیال ہو کہ آپ میں کوئی تبدیلی آگئی ہو؟ مگر اس حالت کی وجہ نشہ آور ادویات یا الکوحل کا خمار نہ ہو اگر مریض آپکی بات سمجھ نہ پا رہا ہو تو اسے بتائیں کہ خوشی یا موج سے میری مراد: بہت اچھا موڈ، نیند کی بہت کم طلب، سوچوں میں تیزی، نئے خیالات کی بہتاب، کام کرنے کی صلاحیت، امنگ، تخلیقی صلاحیت اور جلد بازی کے برتاو میں اضافہ ہے اگر جواب ہاں میں ہے تو پھر اگلا سوال پوچھیں۔	نہیں	ہاں	1
(b)	کیا آپ آجکل خوشی یا جوش کی کیفیت یا توانائی میں اضافہ محسوس کر رہے ہیں؟	نہیں	ہاں	2
D2 (a)	کیا کبھی ایسا ہوا کہ آپ لگاتار کئی دن تک چڑچڑے پن کا شکار رہے ہوں یہاں تک کہ گھر سے باہر لوگوں سے بحث مباحثہ اور تکرار (تو تو میں میں) کی یا جھگڑا یا مارپیٹ تک نوبت آگئی ہو۔ یا آپ کسی پر چیخے چلائے ہوں؟ کیا آپ کو یا دوسرے لوگوں کو لگا کہ آپ عام لوگوں کی نسبت چڑچڑے یا غصیلے ہو گئے ہیں، چاہے آپ خود کو اس وقت ٹھیک ہی کیوں نہ سمجھ رہے ہوں؟	نہیں	ہاں	3
(b)	اگر ہاں تو کیا آپ آج کل متواتر چڑچڑے پن کا شکار ہیں؟	نہیں	ہاں	4
	کیا D1a اور D2a کا جواب ہاں ہے؟	نہیں←	ہاں	
D3 (a)	اگر D1b اور D2b کا جواب "ہاں" ہے تو صرف "**موجودہ دورے**" کے سوالات کریں۔ اگر D1b اور D2b کا جواب نہیں ہے "**تو ماضی کے دورے کی علامات**" سے متعلق سوالات کریں۔ اس عرصے میں جب آپ بہت خوش باش، توانا یا چڑچڑے ہو گئے تھے تو کیا آپ نے یہ محسوس کیا کہ آپ وہ کچھ کر سکتے ہیں جو دوسرے نہیں کر سکتے یا یہ کہ آپ ایک اہم شخصیت ہیں؟	نہیں	ہاں	5
(b)	آپ نے نیند کی طلب پہلے سے کم محسوس کی، مثلاً چند گھنٹے کی نیند آپ کے لیے کافی تھی؟	نہیں	ہاں	6
(c)	آپ نے یہ محسوس کیا کہ آپ بغیر رکے بہت زیادہ بولنے لگے یا اتنا تیز بولتے ہیں کہ لوگوں کو آپ کی	نہیں	ہاں	7

			بات سمجھنے میں دشواری ہونے لگتی ہے؟	
8	ہاں	نہیں	آپ کے ذہن میں سوچیں تیز تیز آنے لگی ہیں؟	(d)
9	ہاں	نہیں	آپ کی توجہ آسانی سے منتشر ہو جاتی ہے اور کوئی چھوٹی سی بات بھی آپ کی توجہ کھینچ لیتی ہے؟	(e)
10	ہاں	نہیں	آپ میں اتنی تیزی یا جسمانی بے چینی آگئی ہو کہ دوسرے لوگ آپ کے بارے میں فکر مند ہو گئے؟	(f)
11	ہاں	نہیں	آپ مسرت آمیز سرگرمیوں میں اتنے گم ہیں کہ خطرات اور نتائج کی پرواہ ہی نہیں رہی؟ مثلاً شاہ خرچی، خطرناک ڈرائیونگ یا جنسی سرگرمی میں صحیح غلط میں فرق نہ کیا ہو۔ کیا D3 کے تین یا تین سے زائد جوابات 'ہاں' ہیں؟ یا اگر D1a کا جواب "نہیں" ہے تو کیا چار اور اس سے زائد کے جوابات 'ہاں' ہیں؟ (گزشتہ دورہ) اگر D1b کا جواب "نہیں" ہے تو (موجودہ دورہ)	(g)
12	کیا یہ علامات کم سے کم ایک ہفتے تک رہیں؟ اور ان کی وجہ سے گھر، کام کی جگہ پر، سماجی طور پر یا سکول میں نمایاں مشکلات پیش آئیں یا آپ ان مسائل کی وجہ سے ہسپتال میں داخل رہے؟ The episode explored WASA: ہاں → Manic Episode نہیں → Hypomanic Episode کیا D4 کا جواب "نہیں" ہے؟ Specify if the Episode is current or past: نہیں ہاں Hypomanic Episode ☐ موجودہ ☐ گزشتہ کیا D4 کا جواب "ہاں" ہے؟ نہیں ہاں Manic Episode ☐ موجودہ ☐ گزشتہ			D4

(E. Panic Disorder)

گھبراہٹ کا حملہ

←اس کا مطلب ہے کہ E5 میں "نہیں" پر نشان لگائیں اور F1 کو چھوڑ دیں

				نمبر شمار
1	ہاں	نہیں	کیا آپ پر ایک سے زیادہ مرتبہ کوئی ایسی کیفیت طاری ہوئی جب آپ کو اچانک گھبراہٹ، خوف یا بے سکونی اور بے آرامی محسوس ہوئی؟ حتیٰ کہ ان حالتوں میں زیادہ تر لوگ ویسا محسوس نہیں کرینگے؟	E1 (a)
2	ہاں	نہیں	کیا یہ دورے دس منٹ میں اپنی انتہا کو پہنچ جاتے تھے؟	(b)
3	ہاں	نہیں	کیا کبھی ایسا بھی ہوا کہ اس طرح کا کوئی حملہ یا دورہ بلا وجہ یا بغیر پیشگی علامات کے، خلاف توقع اچانک ہو جائے؟	E2
4	ہاں	نہیں	کیا کبھی ایسا ہوا کہ ایسے دورے کے بعد ایک ماہ یا اس سے زیادہ عرصے تک آپ کو یہ خدشہ رہا ہو کہ ایسا دورہ دوبارہ نہ ہو جائے یا آپ اس دورے کے نتائج کے بارے میں فکر مند رہے ہوں؟	E3
			سب سے شدید دورہ جو آپ کو یاد ہو اس کے دوران:	E4
5	ہاں	نہیں	اس میں دل کی بہت زیادہ اور تیز دھڑکن محسوس ہوئی یا دل ڈوبنے لگا؟	(a)
6	ہاں	نہیں	کیا آپ کو بہت زیادہ پسینہ آیا یا ہاتھ ٹھنڈے ہو گئے؟	(b)
7	ہاں	نہیں	کیا آپ پر رعشہ یا کپکپی طاری ہوئی؟	(c)
8	ہاں	نہیں	کیا آپ کو سانس پھولنے یا سانس لینے میں مشکل کا احساس ہوا؟	(d)
9	ہاں	نہیں	کیا آپ کا دم گھٹنے لگا یا گلے میں کوئی چیز پھنسی ہوئی محسوس ہونے لگی؟	(e)
10	ہاں	نہیں	کیا آپ کو سینے میں درد، دباو، گھٹن یا بوجھ محسوس ہونے لگا؟	(f)
11	ہاں	نہیں	کیا آپ نے متلی، پیٹ میں گڑبڑ محسوس کی یا اچانک دست لگ گئے؟	(g)
12	ہاں	نہیں	کیا آپ کو چکر آنے لگے، پیر لڑکھڑانے لگے یا غشی طاری ہو گئی؟	(h)
13	ہاں	نہیں	کیا آپ کو اپنے اردگرد چیزیں عجیب، مصنوعی یا خود سے جدا، غیر مانوس، اپنا جسم یا اسکا کوئی حصہ خود سے جدا محسوس ہوا؟	(i)

مترجمان: فاروق نعیم، محمد ایوب، اسد ربانی شاہ، مہوش خالد، ناشران: لاہور انسٹیٹیوٹ آف ریسرچ اینڈ ڈیولپمنٹ، لاہور، پاکستان

(j)	کیا آپ کو یہ ڈر لگا کہ آپ اپنے اوپر قابو نہیں رکھ سکیں گے یا پاگل ہو جائیں گے؟	نہیں	ہاں	14
(k)	کیا آپ کو موت کا خوف آنے لگا؟	نہیں	ہاں	15
(l)	کیا آپ کو جسم یا جسم کے کچھ حصوں میں چبھن یا بے حسی کا احساس ہونے لگا یا سوئیاں چبھنے لگیں؟	نہیں	ہاں	16
(m)	کیا آپ کو بہت زیادہ گرمی یا سردی لگنے لگی تھی؟	نہیں	ہاں	17
E5	کیا E3 اور E4 کے چار سے زیادہ جواب ہاں ہیں؟	نہیں	ہاں→E4 گھبراہٹ کا حملہ زندگی بھر کے لیئے	
E6	اگر E5 کا جواب 'نہیں' ہے تو کیا E4 میں سے کسی ایک کا جواب ہاں ہے تو پھر F1 کو چھوڑ دیں	نہیں ↓ **Limited Symptom Attack Life time**	ہاں	
E7	کیا پچھلے ماہ میں یہ دورہ متواتر (دو یا زیادہ مرتبہ) ہوا جس کے بعد آپ کو مسلسل یہ دھڑکا لگا رہا ہو کہ یہ دوبارہ ہو جائے گا؟	نہیں ↓ Panic Disorder, Current	ہاں	18

F- Agoraphobia حبس کا ڈر

F1	ہجوم میں یا قطار میں کھڑے ہوئے یا گھر سے دور یا گھر پہ اکیلے ہیں، یا پل پر سے گزرتے ہوئے یا بس، ریل گاڑی یا ویگن وغیرہ میں جہاں سے آپ آسانی سے نہ نکل سکتے ہوں اور آپ کی مدد کے لیے کوئی موجود نہ ہو، تو آپ کو یہ گھبراہٹ یا بے آرامی ہو جاتی ہے کہ آپ کو گھبراہٹ کا دورہ پڑ جائے گا یا گھبراہٹ کی طرح کی علامات جن کا ہم نے ذکر کیا ہونے لگیں؟ اگر F1 کا جواب 'نہیں' ہے تو F2 میں بھی نہیں پر نشان لگائیں۔	نہیں	ہاں	19
F2	کیا آپ ان تمام صورتوں میں اس قدر خوفزدہ ہوتے ہیں کہ ان سے بچنا یا ان کا سامنا کرنے کے لیے آپ کو ایک ساتھی کے سہارے کی ضرورت ہوتی ہے یا پھر ان کے دوران کافی تکلیف کا شکار ہوتے ہیں؟	نہیں ہاں ↓ حبس کا ڈر		20

اگر F2 (حبس کا ڈر، موجودہ) کا جواب "نہیں" ہے اور E7 (گھبراہٹ کا حملہ، موجودہ) کا جواب 'ہاں' ہے تو؛

نہیں ہاں↓
حبس کا ڈر
گھبراہٹ کے حملے کے بغیر، موجودہ

اگر F2 (حبس کا ڈر، موجودہ) کا جواب "ہاں" ہے اور E7 (گھبراہٹ کا حملہ، موجودہ) کا جواب 'ہاں' ہے تو؛

نہیں ہاں↓
حبس کا ڈر
گھبراہٹ کے حملے کے ساتھ، موجودہ

اگر F2 (حبس کا ڈر، موجودہ) کا جواب "ہاں" ہے اور E5 (گھبراہٹ کا حملہ، زندگی بھر کے لیئے) کا جواب 'نہیں' ہے تو؛

نہیں ہاں↓
حبس کا ڈر، موجودہ
گھبراہٹ کے حملے کے بیان کے بغیر

G. Social Phobia (Social Anxiety Disorder)

سماجی میل جول کا ڈر

←Diagnosisپر جائیں اور تمام تشخیصی خانوں میں 'نہیں' پر نشان لگائیں اور اگلے Moduleپر چلے جائیں۔

نمبر شمار				
G1	پچھلے ماہ میں کیا آپ کو یہ فکر یا اندیشہ تھا کہ لوگ آپ کو دیکھ رہے ہیں؟ یا آپ لوگوں کو توجہ کا مرکز ہیں؟ یا یہ کہ لوگ آپ کی تذلیل کریں گے؟ مثلاً جب آپ لوگوں کے سامنے تقریر کر رہے ہوں یا بات کر رہے ہوں یا باہر کسی مجمع (شادی بیاہ، ہوٹل وغیرہ) میں کھانا کھاتے ہوئے یا دوسروں کے سامنے کچھ پڑھ لکھ رہے ہوں یا ویسے ہی لوگوں کے درمیان ہوں؟	نہیں←	ہاں	1
G2	کیا یہ خوف بہت زیادہ ہے اور بلا وجہ یا نامعقول ہے؟	نہیں←	ہاں	2
G3	کیا آپ ان تمام حالات سے اس قدر خوفزدہ رہتے ہیں کہ ان سے کنارہ کشی کرتے ہیں اور اگر نہ بچ سکیں تو اذیت محسوس کرتے ہیں؟	نہیں←	ہاں	3
G4	کیا اس خوف سے آپ کے روزمرہ کے کام کاج یا معاشرتی میل جول میں رکاوٹ پیدا ہوتی ہے یا یہ خوف آپکے لئے بہت زیادہ تکلیف کا باعث بنتا ہے؟ نہیں ہاں سماجی میل جول کا ڈر، موجودہ			4

وسوسوں اور جبری افعال کا ڈر

(H. Obsessive Compulsive Disorder)

نمبر شمار	←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔			
H1	پچھلے مہینے کے دوران کیا آپ کو کوئی وسوسہ یا سوچیں، تحریکیں، تصورات یا کوئی خاص تصور ذہن میں آکر بار بار ستاتا رہتا تھا۔ جو آپ کی مرضی کے خلاف ہو، ناخوشگوار اور غیر مناسب ہو یا زبردستی دماغ میں داخل ہوتا ہو اور آپکے لیئے تکلیف دہ ہو؟ مثلاً یہ خیال کہ آپ گندے ہیں، یا یہ خوف کہ آپکو جراثیم لگ جائیں گے یا آپ سے دوسروں کو لگ جائیں گے یا آپ کسی کو نا چاہتے ہوئے بھی نقصان پہنچادیں گے۔ یا یہ خوف کہ آپ ان سوچوں پر جلدبازی میں عمل کر بیٹھیں گے یا یہ خوف کہ کسی قسم کی غلطی کے ذمہ دار آپ ہونگے یا جنسی نوعیت کے وسوسے، تصور اور تحریکات یا چیزیں اکٹھی کرنا یا مذہبی وسوسے وغیرہ۔	نہیں← H4	ہاں	1
H2	کیا دھیان ہٹانے اور چھٹکارا حاصل کرنے کی کوششوں کے باوجود یہ وسوسے آپ کے ذہن میں بار بار آجاتے ہیں؟	نہیں← H4	ہاں	2
H3	کیا آپ یہ سمجھتے ہیں کہ وسوسے آپ کے اپنے ذہن کی پیداوار ہیں۔ اور آپ پر باہر سے مسلط نہیں کیے جارہے ہیں؟	نہیں	ہاں← وسوسے	3
H4	پچھلے ماہ کے دوران کیا آپ کو کوئی کام بار بار کرنا پڑا جبکہ آپ نے روکنے کی کوشش کی مگر رک نہ سکے اور مجبور ہوگئے، جیسے بار بار دھلائی یا صفائی کرنا، چیزوں کا بار بار گننا، یا چیک کرنا یا دہرانا، چیزوں کو اکٹھا کرنا، خاص ترتیب سے رکھنا۔ یا اسی طرح کے کوئی دوسرے توہماتی مناسک؟	نہیں	ہاں← جبری افعال	4
	کیا "H3" اور H4 کا جواب "ہاں" ہے؟	نہیں←	ہاں	
H5	کیا آپ نے محسوس کیا کہ یہ وسوسے اور سوچیں اور جبری برتاو بہت زیادہ اور غیر معقول ہیں۔	نہیں←	ہاں	5
H6	کیا یہ وسوسوں کی سوچوں اور جبری برتاو سے آپ کے روز کے معمولات یا پیشہ ورانہ کارکردگی یا معمول کا میل جول یا تعلقات متاثر ہوئے ہیں یا یہ آپ کا ایک دن میں ایک گھنٹے سے زیادہ وقت لے لیتے ہیں؟			6

وسوسوں اور جبری افعال کا ڈر، موجودہ	ہاں	نہیں

بعد از صدمہ دباؤ (باصد) کا عارضہ (اختیاری)

I. Posttraumatic Stress Disorder (Optional)

←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔

نمبر شمار				
I.1	کیا کبھی آپ کو ایسا واقعہ پیش آیا یا آپ نے دیکھا یا اس میں کسی طرح ملوث ہوئے جو کہ ہولناک ہو، جس میں کسی کی جان چلی گئی ہو، یا ایسا ہونے کا شدید امکان ہو یا آپ یا کوئی اور شدید زخمی ہوگیا ہو؟ مثلاً کوئی بڑا حادثہ، جنسی یا جسمانی حملہ، دہشت گردی کا واقعہ یا کسی نے یرغمال بنالیا ہو یا اغوا کر لیا ہو، آگ لگ گئی ہو، کوئی لاش دیکھی ہو، کسی عزیز یا دوست کی اچانک موت، جنگ یا قدرتی آفت وغیرہ	نہیں←	ہاں	1
I.2	کیا اس واقعے کے نتیجے میں آپ نے شدید خوف، بے بسی یا دہشت محسوس کی؟	نہیں←	ہاں	2
I.3	پچھلے ماہ کے دوران کیا آپ نے اس واقعے کا بہت دردناک طریقے سے دوبارہ تجربہ کیا؟ جیسے ڈراونے خواب کی صورت میں، شدید خیال کی صورت میں یا بطور یاد ماضی یا کوئی جسمانی علامت یا یہ لگا کہ یہ واقعہ دوبارہ ہو رہا ہے۔ اور آپ کو اس کی وجہ سے اذیت ہوئی۔	نہیں←	ہاں	3
I.4 (a)	پچھلے ماہ کے دوران: کیا آپ نے اس واقعے کے بارے میں سوچنے یا ان تمام چیزوں سے بچنے کی کوشش کی جو آپ کو اس واقعے کی یاد دلاتی ہیں؟	نہیں	ہاں	4
(b)	کیا آپ کو اس واقعے کا کوئی اہم حصہ یا بات یاد کرنے میں مشکل ہوتی ہے؟	نہیں	ہاں	5
(c)	کیا سماجی میل جول اور تفریحی کاموں (مشاغل وغیرہ) میں آپ کی دلچسپی کم ہوگئی ہے؟	نہیں	ہاں	6
(d)	کیا آپ خود کو دوسروں سے الگ اور بیگانہ محسوس کرنے لگے ہیں؟	نہیں	ہاں	7
(e)	کیا آپ کو لگا کہ آپ جزباتی طور پر بے حس ہوگئے ہیں؟	نہیں	ہاں	8
(f)	کیا آپ نے سوچا کہ آپ کی زندگی مختصر ہوگئی ہے یا آپ دوسروں کی نسبت جلد فوت ہو جائیں گے؟	نہیں	ہاں	9
	کیا I.4 کے تین یا زائد جوابات "ہاں" ہیں؟	نہیں←	ہاں	
I.5 (a)	پچھلے مہینے کے دوران: کیا آپ کو سونے میں مشکلات پیش آئیں؟	نہیں	ہاں	10

(b)	کیا آپ خصوصی طور پر بہت چڑچڑے ہوگئے اور شدید غصہ کیا؟	نہیں	ہاں	11
(c)	کیا آپ کو توجہ مرکوز کرنے میں مشکل پیش آئی؟	نہیں	ہاں	12
(d)	کیا آپ مسلسل گھبراتے ہوئے یا چوکنے رہتے تھے؟	نہیں	ہاں	13
(e)	کیا ذرا سی باٹ پر آپ کو جھٹکا لگتا تھا یا آپ حیران ہو جوتے تھے؟	نہیں	ہاں	14
	کیا I.5 کے دو یا زائد جواب "ہاں" ہیں؟	نہیں←	ہاں	
I.6	کیا ان تمام چیزوں کی وجہ سے پچھلے ماہ کے دوران آپ کے کام کاج اور سماجی سرگرمیاں متاثر ہوئیں یا آپ کو خاطر خواہ تکلیف کا سامنا کرنا پڑا؟ نہیں ہاں بعد از صدمہ دباؤ (باصد) کا عارضہ، موجودہ			15

شراب کا زائد استعمال اور انحصار

(K. Alcohol Abuse and Dependence)

←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔

نمبر شمار				
J1	کیا پچھلے 22 ماہ میں تین یا تین سے زیادہ مواقع پر آپ نے تین گھنٹے کے دوران تین یا تین سے زیادہ شراب کے گلاس پیئے؟	نہیں	ہاں	1
J2 (a)	پچھلے 22 ماہ میں: کیا جب آپ نے شراب شروع کی تھی تو جس مقدار سے آپ کو نشہ ہو جاتا تھا اس قدر نشے کے سرور کو حاصل کرنے کے لیے اب آپ کو مقدار بڑھانا پڑتی ہے؟	نہیں	ہاں	2
(b)	کیا جب آپ نے شراب پینا کم کرنے کی کوشش کی تو آپ کے ہاتھ کانپنے لگے، پسینہ آنے لگا یا آپ کو بے چینی محسوس ہوئی؟ کیا آپ نے ان علاماتوں سے بچنے کے لئے مزید شراب پی؟ (اگر ان میں کوئی بھی علامت ہو تو ہاں پر نشان لگائیں)	نہیں	ہاں	3
(c)	جب آپ نے شراب پی تو جتنی مقدار میں آپ نے پینے سے پہلے سوچا یا طے کیا تھا کیا بعد میں اس سے زیادہ پی؟	نہیں	ہاں	4
(d)	کیا آپ نے شراب پینا کم کرنے یا چھوڑنے کی کوشش کی مگر ناکام رہے؟	نہیں	ہاں	5
(e)	جن دنوں میں آپ نے شراب پی کیا آپ کا زیادہ وقت شراب حاصل کرنے، پینے اور پھر اس کے اثرات سے نکلنے کی نظر ہو جاتا تھا؟	نہیں	ہاں	6
(f)	کیا آپ نے اپنی اس عادت کی وجہ سے کام کاج، تفریحی مشاغل اور دوسروں کے ساتھ میل جول میں کم وقت گزارا؟	نہیں	ہاں	7
(g)	یہ جانتے ہوئے بھی کہ شراب آپ کی جسمانی اور ذہنی صحت کے لئے مضر ہے آپ نے پینا جاری رکھا؟	نہیں	ہاں	8

کیا "2J" کے تین یا زائد جوابات "ہاں" ہیں؟

	نہیں	ہاں ←
	شراب پر انحصار، موجودہ	

J3 (a)	پچھلے 22 ماہ میں: کیا آپ گھر یا سکول میں، جب آپ پہ ذمہ داریاں تھیں، ایک سے زیادہ مرتبہ خمار یا ترنگ کا شکار ہوئے؟ کیا اس کی وجہ سے کوئی مسئلہ ہوا؟ صرف مسئلہ ہونے پر "ہاں" پر نشان لگائیں	نہیں	ہاں	9
(b)	کیا آپ کو ایسی جگہ پر خمار ہوا جب آپ کی جان کو خطرہ تھا مثلاً گاڑی چلاتے ہوئے، موٹر سائیکل پر سواری کرتے ہوئے، مشینری کا استعمال کرتے ہوئے، کشتی رانی کرتے ہوئے وغیرہ؟	نہیں	ہاں	10
(c)	کیا آپ کو ایک سے زیادہ دفعہ شراب نوشی کی وجہ سے قانونی مسائل کا سامنا کرنا پڑا مثلاً گرفتاری یا نقص امن وغیرہ؟	نہیں	ہاں	11
(d)	کیا خاندان اور دوسرے لوگوں کو اس کی وجہ سے مسائل ہوئے اور اس کے باوجود آپ نے شراب نوشی جاری رکھی؟	نہیں	ہاں	12

کیا "3J" کے ایک یا زائد جواب "ہاں" ہیں؟

	نہیں	ہاں
	شراب کا زائد استعمال، موجودہ	

شراب کے علاوہ دوسری نفسیاتی تاثیری اشیاء کے استعمال کا عارضہ

(K. Non-Alcohol Psychoactive Substance use Disorder)

←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔

				نمبر شمار
			اب میں آپ کو نشہ آور چیزوں کی فہرست دکھانے / پڑھ کے سناتا ہوں۔	K1
	ہاں	نہیں	کیا پچھلے 12 ماہ کے دوران کبھی ایک سے زیادہ مرتبہ ترنگ میں آنے کے لئے یا بہتر محسوس کرنے کے لئے یا اپنے موڈ کو بہتر کرنے کے لئے ان میں سے کسی شے کا استعمال کیا؟ ہر استعمال کی گئی دوائی پر نشان لگائیں۔	(a)

Circle Each Drug Taken

Stimulants: amphetamines, "speed", crystal meth, "rush", Dexedrine, Ritalin, Diet pills.
Cocaine: snorting, IV, freebase, crack, "speedball".
Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.
Hallucinogens: LSD ("acid"), mescaline, peyote, PCP("Angel Dust", "peace pill"), psilocybin, STP, "mushrooms", ecstasy, MDA, or MDMA.
Inhalants: "glue", ethyl chloride, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").
Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".
Tranquilizers: Quaalude, seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, Barbiturates, Miltown.
Miscellaneous: steroids, nonprescription sleep or diet pills, GHB. Any others?
Specify most used drug(s):

Check one box

Only one drug/drug class has been used. ☐
Only the most used drug class is investigated ☐
Only the most used drug class used is examined separately
(photocopy K3 and K3 as needed) ☐
b. specify with drug/drug class will be explored in the interview below if there is
Concurrent or sequential polysubstance: _____

نمبر شمار				
	نشہ یا دوائی کے استعمال کے متعلق بات کرتے ہوئے، پچھلے بارہ ماہ میں:	نہیں	ہاں	1
(a)	کیا آپ کو ایسا لگا کہ آپکو پہلی بار جتنا خمار یا سرور حاصل کرنے کے لیئے اسکی (نشہ یا دوائی کا نام لیں) زیادہ مقدار لینے کی ضرورت ہے؟			
(b)	جب آپ نے یہ نشہ آور شے / اشیاء کا استعمال کم کر دیا یا لینا چھوڑ دیں تو کیا آپ میں ترک کرنے کی کوئی علامت / علامات ظاہر ہوئیں؟ مثلاً بے چینی، جس میں دردیں، کپکپی، بخار، کمزوری، دست لگنا، متلی، پسینہ آنا، دل کا زور زور سے دھڑکنا، نیند نہ آنا، غصہ آجانا، گھبراہٹ ہونا، چڑچڑاپن یا اداسی؟ کیا اس سے بچنے کی خاطر آپ نے کوئی نشہ آور شے استعمال کی تاکہ آپ بہتر محسوس کر سکیں؟ اگر ان میں سے کوئی ہو تو 'ہاں' پر نشان لگائیں	نہیں	ہاں	2
(c)	کیا آپ نے اکثر یہ محسوس کیا کہ آپ بالآخر اپنی سوچ یا طے شدہ مقدار سے زیادہ استعمال کر جاتے تھے؟	نہیں	ہاں	3
(d)	کیا آپ نے اس نشہ یا دوا کی مقدار کم کرنے یا بالکل چھوڑنے کی کوشش کی مگر ناکام رہے؟	نہیں	ہاں	4
(e)	جن دنوں میں آپ نے نشہ آور شے کا استعمال کیا آپ نے کافی وقت نشہ حاصل کرنے، استعمال کرنے اور اس کے متعلق سوچنے اور اثرات سے بحالی میں صرف کیا؟ مثلاً دو گھنٹے سے زیادہ۔	نہیں	ہاں	5
(f)	کیا نشہ کے استعمال کیوجہ سے آپ اپنے کام میں، تفریحی کاموں میں اور گھر اور دوستوں کے ساتھ کم وقت گزارنے لگے تھے؟	نہیں	ہاں	6
(g)	کیا آپ نے نشہ جاری رکھا، حالانکہ اسکی وجہ سے آپکو جسمانی اور ذہنی مسائل کا سامنا کرنا پڑا؟	نہیں	ہاں	7

کیا "K2" کے دو یا زائد جوابات "ہاں" ہیں؟

نہیں ہاں←

نشہ پر انحصار موجودہ

____Specify Drug

K3 (a)	نشہ یا دوائی کے استعمال کے متعلق بات کرتے ہوئے، پچھلے بارہ ماہ میں: کیا آپ کو ایک سے زیادہ مرتبہ خمار، ترنگ (Hangover) ہوا یا اسکی وجہ سے آپ پیشہ ورانہ ذمہ داریاں مثلاً گھر کے کام کاج پوری طرح نہیں کر سکے یا اس وجہ سے کوئی مسئلہ پیدا ہوا؟ (صرف مسئلہ ہونے پر "ہاں" پر نشان لگائیں)	نہیں	ہاں	8
(b)	کیا آپ کو کبھی نشہ کی وجہ سے، ایک سے زیادہ بار، ایسی جگہ پر خمار ہوا جب آپ کی جان کو خطرہ تھا مثلاً گاڑی چلاتے ہوئے، موٹر سائکل پر سواری کرتے ہوئے، مشینری کا استعمال کرتے ہوئے، کشتی رانی کرتے ہوئے وغیرہ؟	نہیں	ہاں	9
(c)	کیا آپ کو ایک سے زیادہ دفعہ نشہ کے استعمال کی وجہ سے قانونی مسائل کا سامنا کرنا پڑا۔ مثلاً گرفتاری یا نقص امن وغیرہ۔	نہیں	ہاں	10
(d)	کیا خاندان اور دوسرے لوگوں کو اس کی وجہ سے مسائل ہوئے اور اس کے باوجود آپ نے نشہ کا استعمال جاری رکھا؟	نہیں	ہاں	11

کیا "K3" کے ایک سے زائد جواب "ہاں" ہیں؟

Specify Drugs_____

نہیں	ہاں
نشہ کا زائد استعمال، موجودہ	

ذہنی اختلال کے عارضے

(L. Psychotic Disorders)

ہر مثبت جواب کی مثالیں دریافت کریں اور اگر مثالیں واضح طور پر سوچ یا ادراکی بگاڑ کی وضاحت کریں یا وہ ثقافتی طور پر نامناسب ہوں تو 'ہاں' پر نشان لگائیں اور نشان لگانے سے پہلے تفتیش کر لیں کہ آیا وہم کے معیار پر اترتے ہیں؟

Delusions are bizarre if, clearly implausibly absurd, not understandable and cannot derived from ordinary life experiences.
Hallucinations are scored bizarre if, a Voice comments on the patients thoughts or behavior or when two or more voices are conversing with each other.

نوٹ: اب ہم آپ سے کچھ ایسے غیر معمولی تجرباٹ کے بارے میں پوچھیں گے جنکا تجربہ بعض لوگ کرتے ہیں

Bizarre				نمبر شمار
ہاں 1	ہاں	نہیں	کیا کبھی آپ کو اس باٹ کا یقین ہوا کہ لوگ آپ کی جاسوسی کر رہے ہیں یا کوئی آپ کے خلاف سازش کر رہا ہے یا آپ کو نقصان پہنچانے کی کوشش کر رہا ہے؟ اگر 'ہاں' تو (مثالوں سے پتہ چلائیں کہ حقیقت کیا ہے)	L.1 (a)
ہاں 2 L6	ہاں←	نہیں	اگر 'ہاں' تو کیا آپکو آج کل بھی ان باتوں پر یقین ہے؟	(b)
ہاں3	ہاں	نہیں	کیا آپ کو کبھی اس باٹ کا یقین رہا کہ کوئی آپ کا ذہن پڑھ رہا ہے یا کوئی آپ کی سوچیں سن سکتا ہے؟ یا آپ خود کسی کا ذہن پڑھ سکتے ہیں یا دوسرے شخص کی سوچیں سن سکتے ہیں؟	L.2 (a)
ہاں4 L6	ہاں←	نہیں	اگر 'ہاں' تو کیا آپ آج کل بھی ان باتوں پر یقین رکھتے ہیں؟	(b)
ہاں5	ہاں	نہیں	کیا آپ کو بھی اس باٹ کا یقین رہا ہے کہ کوئی بیرونی طاقت یا کوئی شخص آپ کے ذہن میں یہ سوچیں داخل کر رہا ہے جو آپ کی اپنی نہیں ہیں یا آپ کو کچھ ایسا کام کرنے پر مجبور کر رہا ہے جو آپ خود اپنی مرضی سے نہیں کرتے؟ یا کبھی آپ کو ایسا لگا کہ آپ پر کسی کا قبضہ، سایہ یا بیرونی طاقت کی گرفت ہے یا آپ میں کوئی حلول کر گیا ہے؟ اگر 'ہاں' تو مثالیں دریافت کریں	L.3 (a)
ہاں6 L6	ہاں←	نہیں	اگر 'ہاں' تو کیا آپ کو آج کل بھی ان باتوں پر یقین ہے؟	(b)

L.4 (a)	کیا کبھی آپ کو ایسا لگا کہ ٹی وی اور ریڈیو یا اخباروں کے ذریعے آپ کو کوئی خصوصی پیغام بھیجا جا رہا ہے، یا کوئی ایسا شخص جو آپ کو نہیں جانتا آپ میں خاص طور پر دلچسپی لے رہا ہے۔	نہیں	ہاں	ہاں7
(b)	اگر 'ہاں' تو کیا آپ کو آج کل بھی ان باتوں پر یقین ہے؟	نہیں	ہاں← L6	ہاں8
L.5 (a)	کیا آپ کے دوستوں یا رشتہ داروں نے کبھی آپ کے اعتقادات اور خیالات کے بارے میں یہ سمجھا کہ وہ غیر معمولی اور عجیب ہیں؟ انٹرویو کرنے والا مثالوں سے دریافت کرے اور صرف جب ہی سوال کا جواب ہاں لکھے اگر اس کے خیالات واضح طور پر وہمی ہوں اور L1 سے L4 میں اسکی وضاحت نہ کی گئی ہو۔ مثال کے طور پر جسمانی اور مذہبی وہم، یا عظمت کا وہم، حسد، احساس جرم، گناہ یا محرومی کا وہم وغیرہ	نہیں	ہاں	ہاں9
(b)	کیا وہ آجکل بھی آپکے اعتقادات، خیالات کے بارے میں یہی رائے رکھتے ہیں؟	نہیں	ہاں	ہاں10
L.6 (a)	کیا آپ کو کبھی ایسی آوازیں سنائی دیں جو دوسروں کو نہ سنائی دیتی ہوں؟ فریکب حسی کو bizarre صرف جب ہوں گے اگر مریض مندرجہ ذیل کا جواب ہاں دے اگر 'ہاں' تو کیا آپ کو کوئی اس طرح کی آواز سنائی دیتی ہے جو آپ کی سوچوں یا برتاو پر تبصرہ کر رہی ہوں یا آپ نے دو یا دو سے زیادہ افراد کو آپس میں باتیں کرتے سنا؟	نہیں	ہاں	11 ہاں
(b)	اگر 'ہاں' تو کیا آپ کو یہ آوازیں پچھلے مہینے میں بھی سنائی دیں؟	نہیں	ہاں← L8b	ہاں12
L.7 (a)	کیا آپ کو کچھ ایسی چیزیں جاگتے میں نظر آئیں جو دوسرے لوگوں کو نظر نہ آتی ہوں؟ انٹرویو کرنے والا مثالوں سے دریافت کرے کہ کیا وہ وہاں کی ثقافت کے لحاظ سے غیر موزوں ہیں؟	نہیں	ہاں	13
(b)	اگر 'ہاں' تو کیا پچھلے ماہ میں بھی کچھ ایسی چیزیں دکھائی دیں؟	نہیں	ہاں	14
معالج کی رائے				
L.8b	کیا مریض میں ابھی بھی بے ربط زبان اور گفتگو یا ربط میں نمایاں بے قاعدگی موجود ہے؟	نہیں	ہاں	15
L.9b	کیا مریض میں ابھی بھی بے کار یا جمودی روّیے موجود ہیں؟	نہیں	ہاں	16

L.10 b	کیا قسام کی منفی علامات جیسے نمایاں کند مزاجی، کم گوئی (حرفی)، یا بامقصد سرگرمیوں کو شروع کرنے اور جاری رکھنے کی نااہلیت ( ) جو انٹرویو کے دوران نمایاں ہو۔	نہیں	ہاں	17
L.11	کیا "یا زائد "b" سوالات کے جوابات "yes bizarre" ہیں؟ یا دو سے زائد "b" سوالات کے جواب محض "ہاں" ہیں؟ (yes Bizarre کی بجائے) نہیں ہاں اختلالِ ذہنی کا عارضہ، موجودہ			
L.12	کیا 1 یا زائد "a" سوالات کے جوابات "Bizarre" کالم میں ہاں ہیں؟ یا دو سے زائد "a" سوالات کے جواب محض "ہاں" ہیں؟ (yes Bizarre کی بجائے) نہیں ہاں اختلالِ ذہنی کا عارضہ، زندگی بھر کے لیئے جانچ لیں کہ کیا دونوں علامات ایک ہی وقت میں نمودار ہوئیں یا کیا L11 کا جواب "ہاں" ہے؟			18
L.13 (a)	کیا L.1b سے L.7b میں سے ایک سے زائد جواب ہاں میں ہیں اور ان میں سے کیا ہے اُداسی کا بڑا دورہ، موجودہ یا مینیا کا دورہ، (موجودہ یا گزشتہ) کا جواب "ہاں" ہے؟	نہیں ←	ہاں	19
(b)	آپ نے مجھے پہلے بتایا تھا کہ آپکو اداسی، ترنگ یا مسلسل چڑچڑے پن کے دورے ہوئے تھے کیا یہ یقین اور تجرباث جو آپ نے بیان کیے اداسی، ترنگ یا چڑچڑے پن کے دورے تک محدود ہے؟ نہیں ہاں مزاجی عارضہ، اختلالِ ذہنی کی علامات کے ساتھ، موجودہ			

(N. Anorexia Nervosa)

عصبی بے اشتہابی

←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔

نمبر شمار				
M1 (a)	آپ کا قد کتنا ہے؟ ---------- فٹ ---------- انچ ---------- سینٹی میٹر			
(b)	پچھلے تین مہینوں میں آپ کا کم سے کم وزن کتنا تھا؟ پونڈ---------- کلوگرام ----------			
(c)	کیا مریض کا وزن جدول میں دیئے گے وزن سے کم ہے جو اسکے قد کے مطابق ہو؟	نہیں	ہاں	
M2	پچھلے تین ماہ میں: کم وزن کے باوجود آپ نے وزن میں اضافے کو روکنے کی کوشش کی؟	نہیں←	ہاں	1
M3	کیا وزن معمول سے کم ہونے کے باوجود آپ کو اپنا وزن زیادہ ہو جانے یا موٹاپے کا خوف لگا رہتا تھا؟	نہیں←	ہاں	2
M4 (a)	کیا آپ کو لگا کہ آپکا جسم موٹا یا جسم کا کوئی خاص حصہ بہت موٹا ہے؟	نہیں	ہاں	3
(b)	کیا آپ کی اپنے بارے میں رائے پر آپ کا وزن اور جسمانی ساخت بہت اثر انداز ہوتی ہے؟	نہیں	ہاں	4
(c)	کیا آپ نے سوچا کہ آپ کا موجودہ وزن مناسب یا زیادہ ہے؟	نہیں	ہاں	5
M5	کیا M4 کے ایک یا ایک سے زائد جوابات ہاں میں؟	نہیں←	ہاں	
M6	صرف خواتین کے لیے: کیا پچھلے 3 ماہ کے دوران آپ کو ماہواری نہیں آئی جبکہ وہ متوقع تھی اور آپ کو حمل بھی نہیں تھا؟	نہیں←	ہاں	6

خواتین کے لیے: کیا M5 اور M6 کا جواب ہاں ہے؟ **مردوں کے لیے:** کیا M5 کا جواب ہاں ہے؟

نہیں	ہاں
عصبی بے اشتہابی، موجودہ	

مترجمان: فاروق نعیم، محمد ایوب، اسد ربانی شاہ، مہوش خالد، ناشران: لاہور انسٹیٹیوٹ آف ریسرچ اینڈ ڈیولپمنٹ، لاہور، پاکستان

وزن کا جدول دیکھیں

TABLE HEIGHT / WEIGHT THRESHOLD (height-without shoes; weight-without clothing)
Female Height/Weight

ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs	84	85	86	87	89	92	94	97	99	102	104	107	110	112
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	38	39	39	40	41	42	43	44	45	46	47	49	50	51

Male Height/Weight

ft/in	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10	5'11	6'0	6'1	6'2	6'3
lbs	105	106	108	110	111	113	115	116	118	120	122	125	127	130	133
cm	155	156	160	163	165	168	170	173	175	178	180	183	185	188	191
kgs	47	48	49	50	51	51	52	53	54	55	56	57	58	59	61

The weight thresholds above are calculated as a 15% reduction below the normal range for the patient's height and gender as required by DSM-IV. This table reflects weights that are 15% lower than the low end of the normal distribution range in the Metropolitan Life Insurance Table of Weights.

(N. Bulimia Nervosa)

عصبی بسیار خوری

←Diagnosis پر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Module پر چلے جائیں۔

				نمبر شمار
7	ہاں	نہیں←	پچھلے تین ماہ میں کیا آپ نے کئی دفعہ اکٹھا بہت زیادہ کھانا کھایا، یا دو گھنٹے کے اندر بے حد مقدار میں کھانا کھایا؟	N1
8	ہاں	نہیں←	پچھلے تین ماہ میں کیا آپ نے ایک ہفتے میں دو یا دو سے زیادہ مقابہ بے حد کھانا کھایا؟	N2
9	ہاں	نہیں←	کیا آپ نے اس دوران محسوس کیا کہ آپکا کھانا آپ کے قابو میں نہیں ہے؟	N3
10	ہاں	نہیں←	کیا آپ نے بے حد کھانے کے اثر کو زائل کرنے کے لئے اس سے ہونے والے وزن میں اضافے کو روکنے کے لیے کچھ اور کیا؟ مثلاً قے کرنا، کھانا کھانا چھوڑ دینا، روزہ رکھنا، ورزش کرنا، قبض کشا دوائیوں کا استعمال، انیما، پیشاپ آور ادویات، یا کوئی دوسری ادویات وغیرہ کا استعمال کرنا	N4
11	ہاں	نہیں←	کیا آپ کی اپنے بارے میں رائے پر آپ کا وزن اور جسمانی ساخت بہت اثر انداز ہوتی ہے؟	N5
skip to N8		ہاں نہیں←	کیا مریض کی علامتیں عصبی بے اشتہابی کے معیار کو پورا کرتی ہیں؟	N6
12	ہاں	نہیں	کیا یہ زیادہ کھانے کے دورے محض اس وقت ہوتے ہیں جب آپ کا وزن ۔۔۔۔ کلو/پاونڈ سے کم ہو؟ Interviewer: write in the above parenthesis the height from the threshold weight for this patient's height/weight table in the anorexia nervosa module.	N7
			کیا N5 کا جواب "ہاں" اور N7 کا "نہیں" ہے یا اسے استعمال نہیں کیا گیا؟ نہیں ہاں عصبی بسیار خوری موجودہ	N8
			کیا N7 کا جواب "ہاں" ہے؟ نہیں ہاں عصبی بے اشتہابی **binge eating/purging type, Current**	

(O. Generalized Anxiety Disorder)

گھبراہٹ کا کل وقتی عارضہ

←Diagnosisپر جائیں اور تمام تشخیصی خانوں میں "نہیں" پر نشان لگائیں اور اگلے Moduleپر چلے جائیں۔

نمبر شمار				
O.1 (a)	کیا پچھلے 6 ماہ کے دوران آپ بہت زیادہ فکر مند رہے یا بہت ساری چیزیں آپ کو پریشان کرتی رہیں؟	نہیں←	ہاں	1
(b)	کیا یہ فکریں اور پریشانیاں دن کا زیادہ تر وقت غالب رہتیں؟	نہیں←	ہاں	2
	کیا مریض کی گھبراہٹ / تشویش خصوصاً کسی ایک چیز تک محدود ہے یا اس سے پہلے بیان کیے گئے کسی عارضے میں اسے زیادہ اچھے طریقے سے بیان کیا جا سکتا ہے؟	نہیں	ہاں←	3
O.2	کیا آپ کے لیئے پریشانیوں کو کنٹرول کرنا مشکل ہو جاتا ہے اور یہ آپ کی توجہ مرکوز کرنے کی صلاحیت میں رکاوٹ ڈالتی ہیں؟	نہیں←	ہاں	4
O.3	اگر اس پوائنٹ سے پہلے دریافت کی گئی بیماریوں میں سے کسی ایک سے یہ علامات منسلک ہیں تو باقی سب سوالات کا جواب نہیں ہوگا۔			
(a)	پچھلے 6 ماہ میں جب آپ بہت زیادہ فکر مند تھے تو کیا اکثر اوقات: آپ بے آرام رہے؟	نہیں	ہاں	5
(b)	آپ تناؤ کا شکار رہے؟	نہیں	ہاں	6
(c)	تھکاوٹ اور کمزوری محسوس کی؟	نہیں	ہاں	7
(d)	توجہ مرکوز کرنے میں مشکل پیش آئی یا ایسا لگا کہ آپ کا ذہن خالی ہوگیا ہے؟	نہیں	ہاں	8
(e)	چڑچڑاپن محسوس کیا؟	نہیں	ہاں	9
(f)	سونے میں مشکل پیش آئی مثلاً نیند دیر سے آئی، آدھی رات کو اٹھ گئے، صبح جلدی بیدار ہو گئے یا نیند پہلے سے زیادہ آنے لگی؟	نہیں	ہاں	10

کیا O3 کے تین یا زائد جواب "ہاں" ہیں؟

نہیں	ہاں
گھبراہٹ کا کل وقتی عارضہ، موجودہ	

غیر سماجی شخصیتی عارضہ (P. Antisocial Personality Disorder)

← تشخیصی خانے میں جائیں اور "نہیں" پر نشان لگائیں

				نمبر شمار
1	ہاں	نہیں	25 سال کی عمر سے پہلے کیا آپ: بار بار سکول سے بھاگے یا گھر سے پوری رات کے لیے باہر رہے	P1 (a)
2	ہاں	نہیں	بار بار جھوٹ بولا، دھوکا دیا، کسی کو ٹھگا یا چوری کی؟	(b)
3	ہاں	نہیں	جھگڑا شروع کیا؟ دوسروں کو ڈرایا دھمکایا یا خوفزدہ کیا؟	(c)
4	ہاں	نہیں	جان بوجھ کر توڑ پھوڑ کی یا آگ لگائی؟	(d)
5	ہاں	نہیں	جان بوجھ کر جانوروں یا لوگوں کو نقصان پہنچایا یا زخمی کیا؟	(e)
6	ہاں	نہیں	کسی کو اپنے ساتھ جنسی فعل کرنے کے لیے مجبور کیا؟	(f)
	ہاں	نہیں←	کیا P1 کے دو یا زائد جوابات "ہاں" ہیں؟	
7	ہاں	نہیں	جب آپ 25 سال کے ہوئے تو کیا آپ نے: ایسا برتاو کئی بار کیا جسے دوسروں نے غیر ذمہ دارانہ سمجھا ہو مثلاً اشیاء کی قیمت جان بوجھ کر نہیں ادا کی جان بوجھ کر جلد بازی کی اور کوئی کام نہیں کیا؟	P2 (a)
8	ہاں	نہیں	کوئی غیر قانونی کام کیا چاہے آپ پکڑے نہ ہی گئے ہوں؟ مثلاً توڑ پھوڑ کرنا، دکان سے چیزیں اچک لینا، چوری کرنا، نشہ بیچنا، قانون کی خلاف ورزی کرنا یا کسی جرم کا ارتکاب کرنا وغیرہ۔	(b)
9	ہاں	نہیں	کئی بار ہاتھا پائی کی (اس میں خاوند/بیوی/بچوں کے ساتھ لڑائی یا مارپیٹ شامل ہے)	(c)
10	ہاں	نہیں	اکثر جھوٹ بولا، دوسروں کو دھوکا دیا یا ٹھگا تاکہ کچھ مالی فائدہ ہو سکے یا محض اپنی خوشی اور شوق کے لیئے جھوٹ بولا	(d)
11	ہاں	نہیں	دوسروں کا خیال کیے بغیر ان کو خطرے میں ڈال دیا؟	(e)
12	ہاں	نہیں	دوسروں کو نقصان پہنچانے بد تمیزی کرنے، جھوٹ بولنے اور توڑ پھوڑ کرنے کے بعد احساس جرم نہیں ہوا؟	(f)
			کیا P2 کے تین یا اس سے زائد جوابات "ہاں" ہیں؟	

نہیں	ہاں
غیر سماجی شخصیتی عارضہ، زندگی بھر کے لیئے	